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(57) Abstract

Methods and kits for detecting polymorphism that are predictive of a subject's susceptibility to developing a chronic obstructive airway disease as well as the relative severity of the disease are described.

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Diagnostics and Therapeutics for Chronic Obstructive Airway Disease

1. BACKGROUND OF THE INVENTION

Asthma is a chronic lung disease characterized by coughing, chest tightness, shortness of breath, and wheezing due to a reversible obstruction of airflow resulting from inflammation and hyper-responsiveness of the airways. In sensitized individuals, inhalation of allergens may produce inflammation of the airway lining, and precipitate a flare-up of asthma. Asthma may also occur as a result of other inflammatory stimuli, such as respiratory tract infections. Individuals who have become sensitized to specific foods may have severely and possibly life-threatening reactions after ingestion of these substances. Asthma, once thought of as a "simple" hypersensitivity reaction, is now known to be a complex condition with a probable spectrum of causes and contributing factors, with airway inflammation as its central attribute. Pulmonary researchers liken it to arteriosclerosis, in the sense that there are many interactive aspects. Many of the contributing factors are now under intensive study, including the chemical reactions that take place in the asthmatic process; the nature of cell-cell communication, the way information is conveyed from one cell or type of cell to another; and the role, reactive or other, of the epithelium. Allergies contribute to both the incidence and severity of asthmatic symptoms. An allergy (also known as immediate hypersensitivity) is defined as an abnormal sensitivity to a substance which is normally tolerated and generally considered harmless, and for which the triggering event is dose-independent, as opposed to a dose-dependent idiosyncratic reaction to a substance. While all immune responses occur as a result of exposure to foreign substances, allergic reactions are distinct from the protective or enhanced "immunity" conferred by immunizations or natural infection. Only about a quarter of the children with asthma outgrow the condition when their airways reach adult size; for the rest, the condition is a lifelong ordeal. The condition persists, according to a research report published by the American Lung Association, in 85 percent of women and in 72 percent of men. (Journal of Allergy and Clinical Immunology Vol. 96:5 11/96).

There were 4,964 deaths from asthma recorded in 1993 in the United States alone. The incidence of asthma mortality in children doubled from 1980 to 1993. Among persons between the ages of 15 and 24 years, the number of deaths rose from 2.5 cases per million in 1980 to 5.2 cases per million in 1993. In 1993, asthma accounted for 342 deaths and approximately 198,000 hospitalization in persons under 25 years of age.

African-Americans account for 21 percent of deaths due to asthma.

African-American children are four times more likely to die of asthma than Caucasian children. African-American males between the ages of 15 and 24 have the highest risk of mortality.

5 A positive family history tends to be one of the strongest risk factors associated with asthma. Positive identification though, can be difficult. Asthma may coexist with other conditions such as congenital abnormalities, infectious conditions, and cystic fibrosis. Additional indicators are considered when the history is atypical or the response to good medical management is poor. Physicians with less experience in the management of this disease may treat these symptoms as an infection, not realizing that the underlying cause is
10 asthma.

The identification of asthma in children relies heavily on the parents' observations for clinical clues. Correct identification requires an asthma and allergy specialist who recognizes the uniqueness of childhood asthma. More subtle signs of asthma, such as chest tightness, may be overlooked, particularly by children. Recurrent or constant coughing
15 spells may be the only common observable symptoms of asthma in young children. Although, demonstration of a favorable clinical response to bronchodilator therapy can help confirm the presence of asthma.

20 There is a tremendous need for early identification of those who are generally susceptible to asthma. Because COAD is a chronic and progressive disease when untreated, early identification would facilitate the administration of appropriate treatment at the earliest stage, thereby increasing the probability of a positive outcome

2. SUMMARY OF THE INVENTION

25 In one aspect, the invention features assays for determining a subject's susceptibility to developing chronic obstructive airway disease or prognosticating on the rapidity and/or ultimate progression of chronic obstructive airway disease in that subject. In one embodiment, the method comprises the step of genotyping a nucleic acid sample obtained from the subject to determine at least one allele of an IL-1 proinflammatory haplotype.

30 For example, an allele of an IL-1 proinflammatory haplotype can be detected by: 1) performing a hybridization reaction between the nucleic acid sample and a probe or probes that are capable of hybridizing to an allele of an IL-1 haplotype in the subject; 2) sequencing at least a portion of at least one allele of an IL-1 haplotype; or 3) determining the electrophoretic mobility of at least one allele of an IL-1 haplotype or a component thereof. In another preferred embodiment, a component of an IL-1 haplotype is subject to an
35 amplification step, prior to performance of the detection step. Preferred amplification steps

are selected from the group consisting of: the polymerase chain reaction (PCR), the ligase chain reaction (LCR), strand displacement amplification (SDA), cloning, and variations of the above (e.g. RT-PCR and allele specific amplification). In a particularly preferred embodiment, the sample is hybridized with a set of primers, which hybridize 5' and 3' to a sense or antisense sequence of an allele of an IL-1 haplotype and is subject to a PCR amplification.

In another aspect, the invention features kits for performing the above-described assays. The kit can include DNA sample collection means and a means for determining at least one allele of an IL-1 haplotype of the subject. The kit may also comprise control samples or standards.

Information obtained using the assays and kits described herein (alone or in conjunction with information on another genetic defect or environmental factor, which contributes to chronic obstructive airway disease) is useful for predicting whether a subject is likely to develop chronic obstructive airway disease. In addition, the information alone or in conjunction with information on another genetic defect contributing to chronic obstructive airway disease (the genetic profile of chronic obstructive airway disease) allows customization of therapy to the individual's genetic profile. For example, this information can enable a doctor to: 1) more effectively prescribe a drug that will address the molecular basis of the cascade resulting in chronic obstructive airway disease; and 2) better determine the appropriate dosage of a particular drug for the particular patient. The ability to target patient populations expected to show the highest clinical benefit, can enable: 1) the repositioning of marketed drugs with disappointing market results; 2) the rescue of drug candidates whose clinical development has been discontinued as a result of safety or efficacy limitations, which are patient subgroup-specific; and 3) an accelerated and less costly development for drug candidates and more optimal drug labeling.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

3. BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the DNA sequence of the human IL-1A gene (GenBank Accession No. X03833).

Figure 2 shows the DNA sequence of the human IL-1B gene (GenBank Accession No. X04500).

Figure 3 shows the DNA sequence of the human IL1-RN gene (GenBank Accession No. X64532).

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 Definitions

For convenience, the meaning of certain terms and phrases employed in the specification, examples, and appended claims are provided below.

The term "allele" refers to alternative forms of a gene at a particular marker. When a subject has two identical alleles, the subject is said to be homozygous. When a subject has two different alleles, the subject is said to be heterozygous.

"Chronic obstructive lung disease" or "chronic obstructive airway disease" (COAD) are terms used to describe a complex of conditions that have in common airflow limitation or airflow obstruction. COAD includes asthma, emphysema, chronic bronchitis, and chronic bronchiolitis. The sites of airway obstruction in COADs vary from the upper airways to the most peripheral bronchioles. The exact cause of most diseases of the airways is not well understood. The definition of airway diseases add to the confusion. Chronic bronchitis is defined clinically by the chronic presence of cough and sputum production. Emphysema, on the other hand, is defined anatomically, on the basis of the breakdown of lung tissue and the enlargement of the alveolar sacs. COADs all have airway narrowing as a disease parameter and they also share inflammation as a component of the disease process.

"Genotyping" refers to the analysis of an individual's genomic DNA (or a nucleic acid corresponding thereto) to identify a particular disease causing or contributing mutation or polymorphism, directly or based on detection of a mutation or polymorphism (a marker) that is in linkage disequilibrium with the disease causing or contributing gene.

The term "haplotype" refers to a set of alleles that are inherited together as a group (are in linkage disequilibrium). As used herein, haplotype is defined to include those

haplotypes that occur at statistically significant levels ($p_{\text{corr}} \leq 0.05$). As used herein, the phrase “an IL-1 haplotype” refers to a haplotype in the IL-1 loci including alleles of the IL-1A, IL-1B and IL-1RN genes and markers in disequilibrium therewith. “Proinflammatory IL-1
5 haplotype” refers to a haplotype that is associated with an excess of proinflammatory release and/or activity (e.g upregulation of functional IL-1 α and/or IL-1 β and/or downregulation of a functional IL-1 receptor antagonist).

“Linkage disequilibrium” refers to co-inheritance of two alleles at frequencies greater than would be expected from the separate frequencies of occurrence of each allele in a given control population. The expected frequency of occurrence of two alleles that are
10 inherited independently is the frequency of the first allele multiplied by the frequency of the second allele. Alleles that co-occur at expected frequencies are said to be in “linkage equilibrium”.

Examples of polymorphic markers in linkage disequilibrium include: the IL-1B allele 2 (-511), IL-1A allele 4(222/223), IL-1A allele 1(gz5/gz6), IL-1A allele 1(-889), the IL-
15 1B allele 2 (+6912), IL-1B allele 1 (+3954), IL-1B/ IL-1RN intergenic region (gaat.p33330) and (Y31), IL-1RN allele 2 (+2018), IL-1RN allele 2 (VNTR) and three polymorphisms that are in linkage disequilibrium with IL-1RN allele 2 (VNTR), (See Clay et al., (1996) *Hum Genet* 97:723-726).

The term “polymorphism” refers to the coexistence of more than one form of a gene or portion (e.g., allelic variant) thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a “polymorphic region of a gene”. A polymorphic region can be a single nucleotide, the identity of which differs in different alleles. A polymorphic region can also be several nucleotides long.

4.2 Predictive Medicine

4.2.1. *Prognostic Assays and Kits*

Based on the findings described in detail in the following examples, the IL-1B allele 2 (+3954) and IL-1B allele 2 (-511) are significantly associated with asthma, the present invention provides methods and kits for determining whether a subject has or is likely to develop a chronic obstructive airway disease and/or for predicting the extent or progression of
30 such a disease in a subject.

In one embodiment, the method comprises genotyping a nucleic acid sample obtained from the subject to detect at least one allele of an IL-1 proinflammatory haplotype. For example, an allele of an IL-1 proinflammatory haplotype can be detected, for example, by determining the transcription rate or mRNA and/or protein level of an IL-1 gene or protein,
35 such as by Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR),

in situ hybridization, immunoprecipitation, Western blot hybridization, or immunohistochemistry. According to one method, cells are obtained from a subject and the IL-1 protein or mRNA level is determined and compared to the level of IL-1 protein or mRNA level in a healthy subject.

5 In another embodiment, the method comprises measuring at least one activity of an IL-1 protein. For example, the constant of affinity of an IL-1 α or β protein of a subject with a receptor can be determined. The results obtained can then be compared with results from the same analysis performed on a subject, who is known to have a chronic obstructive airway disease.

10 In preferred embodiments, the method is characterized as comprising genotyping a nucleic acid sample obtained from the subject to determine at least one allele of an IL-1 proinflammatory haplotype. In an exemplary embodiment, there is provided a nucleic acid composition comprising a nucleic acid probe including a region of nucleotide sequence which is capable of hybridizing to a sense or antisense sequence of at least one allele of an IL-1
15 proinflammatory haplotype. For example, the nucleic acid can be rendered accessible for hybridization, the probe contacted with the nucleic acid of the sample, and the hybridization of the probe to the sample nucleic acid detected. Such technique can be used to detect alterations or allelic variants at either the genomic or mRNA level as well as to determine mRNA transcript levels.

20 A preferred detection method is allele specific hybridization using probes overlapping a region of at least one allele of an IL-1 proinflammatory haplotype and having about 5, 10, 20, 25, or 30 nucleotides around the mutation or polymorphic region. In a preferred embodiment of the invention, several probes capable of hybridizing specifically to other allelic variants involved in a chronic obstructive airway disease are attached to a solid
25 phase support, e.g., a "chip" (which can hold up to about 250,000 oligonucleotides). Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described e.g., in Cronin et al. (1996) Human Mutation 7:244. In one embodiment, a chip comprises all the allelic variants of at least one polymorphic region
30 of a gene. The solid phase support is then contacted with a test nucleic acid and hybridization to the specific probes is detected. Accordingly, the identity of numerous allelic variants of one or more genes can be identified in a simple hybridization experiment.

35 These techniques may also comprise the step of amplifying the nucleic acid before analysis. Amplification techniques are known to those of skill in the art and include, but are not limited to cloning, polymerase chain reaction (PCR), polymerase chain reaction of

specific alleles (ASA), ligase chain reaction (LCR), nested polymerase chain reaction, self sustained sequence replication (Guatelli, J.C. et al., 1990, Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. et al., 1989, Proc. Natl. Acad. Sci. USA 86:1173-1177), and Q-Beta Replicase (Lizardi, P.M. et al., 1988, Bio/Technology 6:1197).

Particularly preferred primers for use in a PCR reaction include:

5' CTC AGG TGT CCT CGA AGA AAT CAA A 3' (SEQ ID No:1)
 5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No:2)
 5' TGG CAT TGA TCT GGT TCA TC-3' (SEQ ID No:3)
 5' GTT TAG GAA TCT TCC CAC TT-3' (SEQ ID No:4)
 5'-CTC.AGC.AAC.ACT.CCT.AT-3' (SEQ ID NO. 5)
 5'-TCC.TGG.TCT.GCA.GCT.AA-3' (SEQ ID NO. 6)
 5'-CTA TCT GAG GAA CAA ACT AGT AGC-3' (SEQ ID NO. 7)
 5'-TAG GAC ATT GCA CCT AGG GTT TGT -3' (SEQ ID NO. 8)
 5'-AAG CTT GTT CTA CCA CCT GAA CTA GGC.-3' (SEQ ID NO. 9)
 5'-TTA CAT ATG AGC CTT CCA TG.-3' (SEQ ID NO. 10)
 5' ACC TAT CTT CTT CGA CAC ATG GGA 3' (SEQ ID No:11);
 5' ACC TAT CTT CTT TGA CAC ATG GGA 3' (SEQ ID No:12);
 5' ATC CCA TGT GTC GAA GAA GAT AGG 3' (SEQ ID No:13);
 5' ATC CCA TGT GTC AAA GAA GAT AGG 3' (SEQ ID No:14);
 5' GAG AGC TCC CGA GGC AGA GAA CAG 3' (SEQ ID No:15);
 5' GAG AGC TCC TGA GGC AGA GAA CAG 3' (SEQ ID No:16);
 5' CTG TTC TCT GCC TCA GGA GCT CTC 3' (SEQ ID No:17); and
 5' CTG TTC TCT ACC TCA GGA GCT CTC 3' (SEQ ID No:18).

Amplification products may be assayed in a variety of ways, including size analysis, restriction digestion followed by size analysis, detecting specific tagged oligonucleotide primers in the reaction products, allele-specific oligonucleotide (ASO) hybridization, allele specific 5' exonuclease detection, sequencing, hybridization, and the like.

PCR based detection means can include multiplex amplification of a plurality of markers simultaneously. For example, it is well known in the art to select PCR primers to generate PCR products that do not overlap in size and can be analyzed simultaneously.

Alternatively, it is possible to amplify different markers with primers that are differentially labeled and thus can each be differentially detected. Of course, hybridization based detection means allow the differential detection of multiple PCR products in a sample. Other techniques are known in the art to allow multiplex analyses of a plurality of markers.

5 In a merely illustrative embodiment, the method includes the steps of (i) collecting a sample of cells from a patient, (ii) isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, (iii) contacting the nucleic acid sample with one or more primers which specifically hybridize 5' and 3' to at least one allele of an IL-1 proinflammatory haplotype under conditions such that hybridization and amplification of the allele occurs, and
10 (iv) detecting the amplification product. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In a preferred embodiment of the subject assay, the allele of an IL-1 proinflammatory haplotype is identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or
15 more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the allele. Exemplary sequencing reactions include those based on techniques developed by Maxim and Gilbert (*Proc. Natl Acad Sci USA* (1977) 74:560) or Sanger (Sanger et al (1977) *Proc. Nat. Acad. Sci* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures may be utilized when performing the subject assays (*Biotechniques* (1995) 19:448), including sequencing by mass spectrometry (see, for example PCT publication WO 94/16101; Cohen et al. (1996) *Adv Chromatogr* 36:127-162; and Griffin et al. (1993) *Appl Biochem Biotechnol* 38:147-159). It will be evident to one of
20 skill in the art that, for certain embodiments, the occurrence of only one, two or three of the nucleic acid bases need be determined in the sequencing reaction. For instance, A-track or the like, e.g., where only one nucleic acid is detected, can be carried out.

In a further embodiment, protection from cleavage agents (such as a nuclease, hydroxylamine or osmium tetroxide and with piperidine) can be used to detect mismatched
30 bases in RNA/RNA or RNA/DNA or DNA/DNA heteroduplexes (Myers, et al. (1985) *Science* 230:1242). In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes formed by hybridizing (labelled) RNA or DNA containing the wild-type allele with the sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to base pair mismatches between
35 the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase

and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on
5 denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton et al (1988) *Proc. Natl Acad Sci USA* 85:4397; Saleeba et al (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes). For example, the mutY enzyme of *E. coli* cleaves A at G/A
10 mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu et al. (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on an allele of a proinflammatory haplotype is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme,
15 and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, for example, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify IL-1 β allele 2 (-511). For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type
20 nucleic acids (Orita et al. (1989) *Proc Natl. Acad. Sci USA* 86:2766, see also Cotton (1993) *Mutat Res* 285:125-144; and Hayashi (1992) *Genet Anal Tech Appl* 9:73-79). Single-stranded DNA fragments of sample and control IL-1 β alleles (-511) are denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a
25 single base change. The DNA fragments may be labelled or detected with labelled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) *Trends Genet*
30 7:5).

In yet another embodiment, the movement of alleles in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a
35 GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further

embodiment, a temperature gradient is used in place of a denaturing agent gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

5 Examples of other techniques for detecting alleles include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation or nucleotide difference (e.g., in allelic variants) is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) *Nature* 324:163); Saiki et al (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele
10 specific oligonucleotide hybridization techniques may be used to test one mutation or polymorphic region per reaction when oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations or polymorphic regions when the oligonucleotides are attached to the hybridizing membrane and hybridized with labelled target DNA.

Alternatively, allele specific amplification technology which depends on selective
15 PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation or polymorphic region of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner
20 (1993) *Tibtech* 11:238. In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making
25 it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

In another embodiment, identification of the allelic variant is carried out using an oligonucleotide ligation assay (OLA), as described, e.g., in U.S. Pat. No. 4,998,617 and in Landegren, U. et al., *Science* 241:1077-1080 (1988). The OLA protocol uses two
30 oligonucleotides which are designed to be capable of hybridizing to abutting sequences of a single strand of a target. One of the oligonucleotides is linked to a separation marker, e.g., biotinylated, and the other is detectably labeled. If the precise complementary sequence is found in a target molecule, the oligonucleotides will hybridize such that their termini abut, and create a ligation substrate. Ligation then permits the labeled oligonucleotide to be recovered using
35 avidin, or another biotin ligand. Nickerson, D. A. et al. have described a nucleic acid detection

assay that combines attributes of PCR and OLA (Nickerson, D. A. et al., Proc. Natl. Acad. Sci. (U.S.A.) 87:8923-8927 (1990). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA.

Several techniques based on this OLA method have been developed and can be used to detect alleles of an IL-1 proinflammatory haplotype. For example, U.S. Patent No. 5,593,826 discloses an OLA using an oligonucleotide having 3'-amino group and a 5'-phosphorylated oligonucleotide to form a conjugate having a phosphoramidate linkage. In another variation of OLA described in Tobe et al. ((1996) Nucleic Acids Res 24: 3728), OLA combined with PCR permits typing of two alleles in a single microtiter well. By marking each of the allele-specific primers with a unique hapten, i.e. digoxigenin and fluorescein, each OLA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

Several methods have been developed to facilitate analysis of single nucleotide polymorphisms. In one embodiment, the single base polymorphism can be detected by using a specialized exonuclease-resistant nucleotide, as disclosed, e.g., in Mundy, C. R. (U.S. Pat. No.4,656,127). According to the method, a primer complementary to the allelic sequence immediately 3' to the polymorphic site is permitted to hybridize to a target molecule obtained from a particular animal or human. If the polymorphic site on the target molecule contains a nucleotide that is complementary to the particular exonuclease-resistant nucleotide derivative present, then that derivative will be incorporated onto the end of the hybridized primer. Such incorporation renders the primer resistant to exonuclease, and thereby permits its detection. Since the identity of the exonuclease-resistant derivative of the sample is known, a finding that the primer has become resistant to exonucleases reveals that the nucleotide present in the polymorphic site of the target molecule was complementary to that of the nucleotide derivative used in the reaction. This method has the advantage that it does not require the determination of large amounts of extraneous sequence data.

In another embodiment of the invention, a solution-based method is used for determining the identity of the nucleotide of a polymorphic site. Cohen, D. et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087). As in the Mundy method of U.S. Pat. No. 4,656,127, a primer is employed that is complementary to allelic sequences immediately 3' to a polymorphic site. The method determines the identity of the nucleotide of that site using labeled dideoxynucleotide derivatives, which, if complementary to the nucleotide of the polymorphic site will become incorporated onto the terminus of the primer.

An alternative method, known as Genetic Bit Analysis or GBATM is described by Goelet, P. et al. (PCT Appln. No. 92/15712). The method of Goelet, P. et al. uses mixtures of labeled terminators and a primer that is complementary to the sequence 3' to a polymorphic site. The labeled terminator that is incorporated is thus determined by, and complementary to, the nucleotide present in the polymorphic site of the target molecule being evaluated. In contrast to the method of Cohen et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087) the method of Goelet, P. et al. is preferably a heterogeneous phase assay, in which the primer or the target molecule is immobilized to a solid phase.

Recently, several primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. et al., Nucl. Acids. Res. 17:7779-7784 (1989); Sokolov, B. P., Nucl. Acids Res. 18:3671 (1990); Syvanen, A. -C., et al., Genomics 8:684-692 (1990); Kuppuswamy, M. N. et al., Proc. Natl. Acad. Sci. (U.S.A.) 88:1143-1147 (1991); Prezant, T. R. et al., Hum. Mutat. 1:159-164 (1992); Ugozzoli, L. et al., GATA 9:107-112 (1992); Nyren, P. et al., Anal. Biochem. 208:171-175 (1993)). These methods differ from GBATM in that they all rely on the incorporation of labeled deoxynucleotides to discriminate between bases at a polymorphic site. In such a format, since the signal is proportional to the number of deoxynucleotides incorporated, polymorphisms that occur in runs of the same nucleotide can result in signals that are proportional to the length of the run (Syvanen, A. -C., et al., Amer.J. Hum. Genet. 52:46-59 (1993)).

For mutations that produce premature termination of protein translation, the protein truncation test (PTT) offers an efficient diagnostic approach (Roest, et. al., (1993) *Hum. Mol. Genet.* 2:1719-21; van der Lijdt, et. al., (1994) *Genomics* 20:1-4). For PTT, RNA is initially isolated from available tissue and reverse-transcribed, and the segment of interest is amplified by PCR. The products of reverse transcription PCR are then used as a template for nested PCR amplification with a primer that contains an RNA polymerase promoter and a sequence for initiating eukaryotic translation. After amplification of the region of interest, the unique motifs incorporated into the primer permit sequential *in vitro* transcription and translation of the PCR products. Upon sodium dodecyl sulfate-polyacrylamide gel electrophoresis of translation products, the appearance of truncated polypeptides signals the presence of a mutation that causes premature termination of translation. In a variation of this technique, DNA (as opposed to RNA) is used as a PCR template when the target region of interest is derived from a single exon.

Any cell type or tissue may be utilized to obtain nucleic acid samples for use in the diagnostics described herein. In a preferred embodiment, the DNA sample is obtained from a bodily fluid, e.g. blood, obtained by known techniques (e.g. venipuncture) or saliva.

Alternatively, nucleic acid tests can be performed on dry samples (e.g. hair or skin). When using RNA or protein, the cells or tissues that may be utilized must express an IL-1 gene.

Diagnostic procedures may also be performed *in situ* directly upon tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents may be used as probes and/or primers for such *in situ* procedures (see, for example, Nuovo, G.J., 1992, PCR *in situ* hybridization: protocols and applications, Raven Press, NY).

In addition to methods which focus primarily on the detection of one nucleic acid sequence, profiles may also be assessed in such detection schemes. Fingerprint profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

Another embodiment of the invention is directed to kits for detecting a predisposition for developing a chronic obstructive airway disease and/or for progressing more rapidly or severely. This kit may contain one or more oligonucleotides, including 5' and 3' oligonucleotides that hybridize 5' and 3' to at least one allele of an IL-1 proinflammatory haplotype. PCR amplification oligonucleotides should hybridize between 25 and 2500 base pairs apart, preferably between about 100 and about 500 bases apart, in order to produce a PCR product of convenient size for subsequent analysis.

For use in a kit, oligonucleotides may be any of a variety of natural and/or synthetic compositions such as synthetic oligonucleotides, restriction fragments, cDNAs, synthetic peptide nucleic acids (PNAs), and the like. The assay kit and method may also employ labeled oligonucleotides to allow ease of identification in the assays. Examples of labels which may be employed include radio-labels, enzymes, fluorescent compounds, streptavidin, avidin, biotin, magnetic moieties, metal binding moieties, antigen or antibody moieties, and the like.

The kit may, optionally, also include DNA sampling means. DNA sampling means are well known to one of skill in the art and can include, but not be limited to substrates, such as filter papers, the AmpliCard™ (University of Sheffield, Sheffield, England S10 2JF; Tarlow, JW, *et al.*, *J. of Invest. Dermatol.* **103**:387-389 (1994)) and the like; DNA purification reagents such as Nucleon™ kits, lysis buffers, proteinase solutions and the like; PCR reagents, such as 10X reaction buffers, thermostable polymerase, dNTPs, and the like; and allele detection means such as the *HinfI* restriction enzyme, allele specific oligonucleotides, degenerate oligonucleotide primers for nested PCR from dried blood.

4.2.2. Pharmacogenomics

Knowledge of the particular IL-1 polymorphisms that are predictive of sepsis, alone or in conjunction with information on other genetic defects contributing to a chronic obstructive airway disease (the genetic profile of the chronic obstructive airway disease) allows a customization of the therapy for a particular disease to the individual's genetic profile, the goal of "pharmacogenomics". For example, subjects having the IL-1B allele 2 (-511) and/or IL-1B allele 2 (+3954) are predisposed to developing a chronic obstructive airway disease or for progressing more rapidly or severely into a chronic obstructive airway disease. Thus, comparison of an individual's IL-1 proinflammatory profile to the population profile for a chronic obstructive airway disease, permits the selection or design of drugs that are expected to be safe and efficacious for a particular patient or patient population (i.e., a group of patients having the same genetic alteration).

The ability to target populations expected to show the highest clinical benefit, based on the IL-1B or disease genetic profile, can enable: 1) the repositioning of marketed asthma drugs with disappointing market results; 2) the rescue of asthma drug candidates whose clinical development has been discontinued as a result of safety or efficacy limitations, which are patient subgroup-specific; and 3) an accelerated and less costly development for asthma drug candidates and more optimal drug labeling (e.g. since the use of markers described herein are useful for optimizing effective dose).

Cells of a subject may also be obtained before and after administration of a therapeutic to detect the level of expression of genes other than IL-1, to verify that the therapeutic does not increase or decrease the expression of genes which could be deleterious. This can be done, e.g., by using the method of transcriptional profiling. Thus, mRNA from cells exposed in vivo to a therapeutic and mRNA from the same type of cells that were not exposed to the therapeutic could be reverse transcribed and hybridized to a chip containing DNA from numerous genes, to thereby compare the expression of genes in cells treated and not treated with the therapeutic.

The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references (including literature references, issued patents, published patent applications as cited throughout this application are hereby expressly incorporated by reference. The practice of the present invention will employ, unless otherwise indicated, conventional techniques, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Molecular Cloning A Laboratory Manual, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: 1989); DNA Cloning, Volumes I and II (D. N. Glover ed., 1985); Oligonucleotide Synthesis (M. J. Gait ed., 1984); Mullis et al. U.S. Patent No:

4,683,195; Nucleic Acid Hybridization(B. D. Hames & S. J. Higgins eds. 1984); Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984).

EXAMPLE 1: Detection of IL-1B (+3954)

The screening of the single base variation (C/T) polymorphism at IL-1B base +3954 was conducted by PCR amplification of genomic templates. One mismatch was inserted in a primer to complete a *TaqI* site as a positive control. The polymorphic *TaqI* site is native. The following primers were produced in an ABI DNA synthesizer based on the genomic sequences (Clark et al., 1986; GENBANK X04500):

5' CTC AGG TGT CCT CGA AGA AAT CAA A 3' (SEQ ID No:1)

5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No:2)

The PCR reaction conditions were as follows:

[95 C (2 minutes)] 1 cycle;

[95 C(1 minute), 67.5 C (1 minute), 74 C (1 minute)] 38 cycles; and

[72 C (8 minutes)] 1 cycle.

Restriction enzyme digestion was conducted at 60°C, for 8 hours. Sizing was by 8% PAGE. The digestion of the PCR product with *Taq I* yields a segment of 12 bp (the absence of which indicates incomplete digestion) and either two further segments of 85 and 97 bp (allele 1), or a single one of 182 bp (allele 2).

EXAMPLE 2: Detection of IL-1B (-511)

The single base polymorphism (C/T) at position - 511 in the IL-1B gene was screened by PCR amplification of genomic templates, followed by RFLP (Restriction Fragment Length Polymorphism) analysis. The gene variation completes an *Ava I* restriction site in the most frequent allele, and a *Bsu 36 I* site in the rarer allele. Hence digestion of the PCR product with these enzymes provides efficient analysis of the IL-1B (-511) locus.

The following primers were produced in an ABI synthesizer based on the genomic sequence (Clark et al, 1986; Genbank X04500):

5' TGG CAT TGA TCT GGT TCA TC-3' (SEQ ID No:3)

5' GTT TAG GAA TCT TCC CAC TT-3' (SEQ ID No:4)

PCR conditions were as follows:

[95 C (1 minute)] 1 cycle

[95 C (1 minute)] 53 C (1 minute), 72 (1 minute)] 35 cycles

[72 C (5 minute)] 1 cycle.

Each PCR reaction was divided in two 25 µl aliquots; one was added to 3 units of *Ava* I, the other to 3.7 units of *Bsu* 36 I, in addition to 3 µl of the specific 10X restriction buffer. Digestion was at 37 °C overnight, sizing was by 9% PAGE. *Ava* I digestion produced 190 + 114 bp segments with allele 1, while allele 2 was uncut (304 bp). The *Bsu* 36 I digestion produced 190 + 114 bp fragments with allele 2, while allele 1 was uncut (304 bp). The restriction pattern obtained was inverted in the two aliquots (identifying homozygotes) or identical (identifying heterozygotes). This protocol provided efficient analysis of the IL-1B (-511) locus.

EXAMPLE 3: Detection of IL-1RN (VNTR)

The existence of a variable number of tandem repeats in intron 2 of IL-1RN gene was first reported during the cloning of the gene (Steinkasserer, A. et al., (1991) *Nucleic Acids Res* 19: 5095). This VNTR was characterised by Tarlow et al ((1993) *Hum Genet.* 91:403-404) as a variable number (2 to 6) of 86 bp repeats. The following primers were produced in an ABI synthesizer based on the genomic sequence (Genbank X64532):

5'-CTC.AGC.AAC.ACT.CCT.AT-3' (+2879/+2895)
(SEQ ID NO. 5)

5'-TCC.TGG.TCT.GCA.GCT.AA-3' (+3274/+3290)
(SEQ ID NO. 6)

The PCR reaction conditions were as follows:

Cycling is performed at [96°, 1 min] x 1 min; 60°C, 1 min; 70°C, 2 min;] x35; [70°, 5 min] x 1; 4°C. Electrophoresis in 2% agarose, 90V, 30 min.

The PCR product sizes are direct indication of number of repeats: the most frequent allele (allele 1) yields a 412 bp product. As the flanking regions extend for 66 bp, the remaining 344 imply four 86 bp repeats. Similarly, a 240 bp product indicates 2 repeats (allele

2), 326 is for 3 repeats (allele 3), 498 is 5 (allele 4), 584 is 6 (allele 6). Frequencies in a North British Caucasian population for the four most frequent alleles are 0.734, 0.241, 0.021 and 0.004.

EXAMPLE 4: Detection of IL-1RN (+2018)

This single base variation (C/T at +2016) in Exon 2 was described by Clay et al. ((1996) *Hum. Genet* 97:723-726). These PCR primers (mismatched to the genomic sequence) was engineered to two enzyme cutting sites on the two alleles. These two alleles are 100% in linkage disequilibrium with the two most frequent alleles of IL-1RN (VNTR). The following primers were produced in an ABI synthesizer based on the genomic sequence (Genbank X04532):

5'-CTA TCT GAG GAA CAA ACT AGT AGC-3' (+1990/+2015)
(SEQ ID NO. 7)

5'-TAG GAC ATT GCA CCT AGG GTT TGT -3' (+2133/+2156)
(SEQ ID NO. 8)

Cycling is performed at [96°, 1 min] x 1; [94°, 1 min; 57°, 1 min; 70°, 2 min;] x35; [70°, 5 min] x 1; 4C. Each PCR reaction is divided in two $\mu\ell$ of the specific 10X restriction buffer. Incubation is at 37°C overnight. Electrophoresis is by PAGE 9%.

The two enzymes cut respectively the two different alleles. *Alu* / will produce 126 + 28 bp fragments for allele 1, while it does not digest allele 2 (154 bp). *Msp* / will produce 125 + 29 bp with allele , while allele 1 is uncut (154 bp). Hence the two reaction s (separated side by side in PAGE) will give inverted patterns of digestion for homozygote individuals, and identical patterns in heterozygotes. Allelic frequencies in a North British Caucasian population are 0.74 and 0.26. For 90% power at 0.05 level of significance in a similar genetic pool, 251 cases should be studied to detect 1.5 fold increases in frequency, or 420 for 0.1 absolute increase in frequency.

EXAMPLE 4: Detection of IL-1A (-889)

The C/T single variation in the IL-1A promoter was described by McDowell et al. (*Arthritis and Rheumatism* 38: 221-228 (1995)). One of the PCR primers has a base change to create an *Nco* I site when amplifying allele 1 (cytosine at -889). The following primers were produced in an ABI synthesizer based on the genomic sequence (Genbank X03833):

5'-AAG CTT GTT CTA CCA CCT GAA CTA GGC.-3' (-967/-945)
(SEQ ID NO. 9)

5'-TTA CAT ATG AGC CTT CCA TG.-3' (-888/-869)
(SEQ ID NO. 10)

MgCl₂ is used at 1mM final, and PCR primers at 0.8 μ M.

Cycling is performed at [96°, 1 min] x 1; 94°, 1 min; 50°, 1 min; 72°, 2 min;] x
45; [72°, 5 min] x 1' 4°C.

Each PCR reaction is added of 6 Units of *Nco* I in addition to μ l of the specific
10X restriction buffer. Incubation is at 37°C overnight. Electrophoresis is by PAGE 6%.

Nco I will produce 83 + 16 for allele 1, while it does not cut allele 2 (99bp.).
Heterozygotes will have the three bands. Allelic frequencies in North English White Caucasian
population are 0.71 and 0.29. For 90% power at 0.05 level of significance in a similar genetic
pool, 214 cases should be studied to detect 1.5 fold increase in frequency, or 446 for 0.1
absolute increase in frequency.

Example 5 Association of IL-1B allele 2 (+3954) and IL-1B allele 2 (-511) With The Presence of Asthma in a Subject

The following study was conducted to evaluate whether there was an
association between asthma and alleles found in the relevant regions of the IL-1B gene. One
hundred six (106) asthma patients were recruited for the study. 251 North British white
Caucasian non-asthmatic subjects were recruited as controls. All asthma patients fulfilled the
ATS criteria for the definition of asthma (*Amer Rev Respir Dis* 1985, 132:180-182.), and
where relevant had a PC20 methacholine of less than 4mg/ml. Asthma patients were clinically
categorized as having either mild or severe asthma. Severe asthma was defined as those
patients requiring more than 800mg/day of inhaled steroids. Asthma patients on beta-2 agonist
alone were categorized as having mild asthma. Of the total number of asthma patients, 50 were
mild asthmatics on beta 2 agonist alone (FEV1 92.5 \pm 1.5% pred) and had a mean age of
26.5 \pm 0.9, and 56 were severe asthmatics on a regimen of at least 800 mg per day of inhaled
steroids (FEV1 58.4 \pm 3.4% pred) with a mean age of 47.2 \pm 2.3. After informed consent was
obtained, 10mls of venous blood was drawn and collected in EDTA-containing tubes from each
patient. Total genomic DNA was extracted and allele frequencies were assessed in DNA

extracted from the 106 patients. For IL-1B (+3954) 105 patients could be genotyped. 104 patients were genotyped for IL-1B (-511). For each DNA, a single PCR product spanning the relevant regions of the IL-1 B gene was produced and analyzed as described in Example 1.

The data were analyzed using the Chi square test to compare carriage of the rare allele (genotypes carrying at least one copy of allele 2 between cohorts). The results for IL-1B (+3954) are presented in the following Table 1 and the results for IL-1B (-511) are presented in the following Table 2.

TABLE 1
IL-1B (+ 3954)

<u>Disease Severity</u>	1.1	1.2	2.2
MILD (N=50)	28	17	5
SEVERE (N=55)	26	24	5
CONTROLS (N=251)	165	81	5
Mild vs Severe	Chi ² =0.497	p=0.48	(N.S.)
"all" vs Control	Chi ² =6.402	p=0.01	O.R.=1.81 (95% C.I.=1.14-2.88)
Severe vs Control	Chi ² =6.557	p=0.01	O.R.=2.14 (95% C.I.=1.19-3.86)

TABLE 2
IL-1B (- 511)

<u>Disease Severity</u>	1.1	1.2	2.2
MILD (N=50)	2	19	3
SEVERE (N=54)	19	31	4
CONTROLS (N=251)	89	129	33
Severe vs Mild	Chi ² =4.541	p=0.033	O.R.=2.34 (95% C.I.=1.06-5.16)
"all" vs Control	Chi ² =2.948	p=0.086	(NS)

As evidenced by Tables 1 and 2, the presence of IL-1B allele 2 (+3954) and IL-1B allele 2 (-511) are significantly associated with clinical asthma. Further, the presence of at least one copy of allele 2 at the IL-1B (-511) locus was found to be associated with more severe disease.

WHAT IS CLAIMED IS:

1. A method for determining a subject's susceptibility to developing chronic obstructive airway disease or for predicting the rapidity or ultimate progression of a chronic obstructive airway disease in the subject, said method comprising the steps of:
 - a) obtaining a nucleic acid sample from the subject; and
 - b) detecting at least one allele of an IL-1 proinflammatory haplotype in said sample, wherein detection of at least one allele of an IL-1 proinflammatory haplotype indicates that the patient has an increased susceptibility to developing chronic obstructive airway disease.
2. A method of claim 1, wherein the at least one allele is IL-1B allele 2 (-511).
3. A method of claim 2, wherein the detecting step comprises amplification using at least one primer selected from the group consisting of:

5' CTC AGG TGT CCT CGA AGA AAT CAA A3' (SEQ ID No:1);

5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No:2);
4. A method of claim 1, wherein the at least one allele is IL-1B allele 2 (+3954).
5. A method of claim 4, wherein the detecting step comprises amplification using at least one primer selected from the group consisting of:

5' TGG CAT TGA TCT GGT TCA TC-3' (SEQ ID No:3);

5' GTT TAG GAA TCT TCC CAC TT-3' (SEQ ID No:4)
6. A method of claim 1, wherein the chronic obstructive airway disease is selected from the group consisting of: asthma, emphysema, chronic bronchitis and chronic bronchiolitis.
7. A method of claim 1, wherein the detecting step comprises amplification using at least one primer selected from the group consisting of:

5'-CTC.AGC.AAC.ACT.CCT.AT-3' (SEQ ID NO. 5)

5'-TCC.TGG.TCT.GCA.GCT.AA-3' (SEQ ID NO. 6)

5'-CTA TCT GAG GAA CAA ACT AGT AGC-3' (SEQ ID NO. 7)

5'-TAG GAC ATT GCA CCT AGG GTT TGT -3' (SEQ ID NO. 8)

5'-AAG CTT GTT CTA CCA CCT GAA CTA GGC.-3' (SEQ ID NO. 9)

5'-TTA CAT ATG AGC CTT CCA TG.-3' (SEQ ID NO. 10)

8. A kit for determining a subject's susceptibility to developing a chronic obstructive airway disease, said kit comprising:

(a) a DNA sample collecting means;

(b) a means for detecting at least one allele of an IL-1 proinflammatory haplotype in the DNA sample.

primer

9. A kit of claim 8, wherein the detection means is comprised of a first that hybridizes 5' or 3' to an allele of an IL-1 proinflammatory haplotype

consisting of:
No:1)

10. A kit of claim 9, wherein the primer is selected from the group
5' CTC AGG TGT CCT CGA AGA AAT CAA A 3' (SEQ ID

5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No:2)

5' TGG CAT TGA TCT GGT TCA TC-3' (SEQ ID No:3)

5' GTT TAG GAA TCT TCC CAC TT-3' (SEQ ID No:4)

5'-CTC.AGC.AAC.ACT.CCT.AT-3' (SEQ ID NO. 5)

5'-TCC.TGG.TCT.GCA.GCT.AA-3' (SEQ ID NO. 6)

5'-CTA TCT GAG GAA CAA ACT AGT AGC-3' (SEQ ID NO. 7)

5'-TAG GAC ATT GCA CCT AGG GTT TGT -3' (SEQ ID NO. 8)

5'-AAG CTT GTT CTA CCA CCT GAA CTA GGC.-3' (SEQ ID NO.

9)

5'-TTA CAT ATG AGC CTT CCA TG.-3' (SEQ ID NO. 10)

haplotype

11. A kit of claim 8, wherein the allele of the IL-1 proinflammatory

is selected from the group consisting of: the IL-1B allele 2 (-511), IL-1A allele 4(222/223), IL-1A allele 1(gz5/gz6), IL-1A allele 1(-889), the IL-1B allele 2 (+6912), IL-1B allele 1 (+3954), IL-1B/ IL-1RN intergenic region

(gaat.p33330)

and (Y31), IL-1RN allele 2 (+2018), IL-1RN allele 2 (+2018)

12. The kit of claim 10, which additionally comprises a second primer that

when hybridizes 3' to an allele of an IL-1 proinflammatory haplotype when the first primer hybridizes 5' and hybridizes 5' to an IL-1 proinflammatory haplotype the first primer hybridizes 3'.

13. The kit of claim 12, wherein said first primer and said second primer hybridize to a region which is in the range of between about 50 and 1000 base pairs.

14. The kit of claim 10, which additionally comprises a detector oligonucleotide.

15. The kit of claim 14, wherein the detector oligonucleotide includes a label.

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Figure 1. DNA Sequence of the human IL-1A gene. (GenBank Accession No. X03833)

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-1437 AAGCTTCTAC CCTAGTCTGG TGCTACACTT ACATTGCTTA CATCCAAGTG TGGTTATTTT
-1377 TGTGGCTCCT GTTATAACTA TTATAGCACC AGGTCTATGA CCAGGAGAAT TAGACTGGCA
-1317 TTAAATCAGA ATAAGAGATT TTGCACCTGC AATAGACCTT ATGACACCTA ACCAACCCCA
-1257 TTATTTACAA TTAAACAGGA ACAGAGGGAA TACTTTATCC AACTCACACA AGCTGTTTTT
-1197 CTCCCAGATC CATGCTTTTT TGCGTTTATT ATTTTTTAGA GATGGGGGCT TCACTATGTT
-1137 GCCCACACTG GACTAAACT CTGGGCCCTCA AGTGATTGTC CTGCCTCAGC CTCCTGAATA
-1077 GCTGGGACTA CAGGGGCATG CCATCACACC TAGTTCATTT CCTCTATTTA AAATATACAT
-1017 GGCTTAAACT CCAACTGGGA ACCCAAACA TTCATTTGCT AAGAGTCTGG TGTTCTACCA
-957 CCTGAAC TAGTGGCCACA GGAATTATAA AAGCTGAGAA ATTCTTTAAT AATAGTAACC
-897 AGGCAACATC ATTGAAGGCT CATATGTA AAAATCCATGCC TTCCTTTCTC CCAATCTCCA
-837 TTCCCAAAC TAGCCACTGG TTCTGGCTGA GGCCTTACGC ATACCTCCCG GGGCTTGCAC
-777 ACACCTTCTT CTACAGAAGA CACACCTTGG GCATATCCTA CAGAAGACCA GGCTTCTCTC
-717 TGGTCCTTGG TAGAGGGCTA CTTTACTGTA ACAGGGCCAG GGTGGAGAGT TCTCTCCTGA
-657 AGCTCCATCC CCTCTATAGG AAATGTGTTG ACAATATTCA GAAGAGTAAG AGGATCAAGA
-597 CTTCTTTGTG CTCAAATACC ACTGTTCTCT TCTCTACCCT GCCCTAACCA GGAGCTTGTC
-537 ACCCCAAACT CTGAGGTGAT TTATGCCTTA ATCAAGCAAA CTTCCCTCTT CAGAAAAGAT
-477 GGCTCATTTT CCCTCAAAAG TTGCCAGGAG CTGCCAAGTA TTCTGCCAAT TCACCCTGGA
-417 GCACAATCAA CAAATTCAGC CAGAACACAA CTACAGCTAC TATTAGAAT ATTATTATTA
-357 ATAAATTCCT CTCCAAATCT AGCCCCTTGA CTTCCGATTT CACGATTTCT CCCTTCCCTC
-297 TAGAACTTG ATAAGTTTCC CGCGCTTCCC TTTTCTAAG ACTACATGTT TGTCATCTTA
-237 TAAAGCAAAG GGTGAATAA ATGAACCAA TCAATAACTT CTGGAATATC TGCAAACAAC
-177 AATAATATCA GCTATGCCAT CTTTCACTAT TTTAGCCAGT ATCGAGTTGA ATGAACATAG
-117 AAAAATACAA AACTGAATTC TTCCCTGTAA ATTCCCCGTT TTGACGACGC ACTTGTAGCC
-57 ACGTAGCCAC GCCTACTTAA GACAATTACA AAAGGCGAAG AAGACTGACT CAGGCTTAAG
4 CTGCCAGCCA GAGAGGGAGT CATTTTCATTG GCGTTTGAGT CAGCAAAGGT ATTGTCTCTA
64 CATCTCTGGC TATTAAAGTA TTTTCTGTTG TTGTTTTTCT CTTTGGCTGT TTTCTCTCAC
124 ATTGCCTTCT CTAAAGCTAC AGTCTCTCCT TTCTTTTCTT GTCCCTCCCT GGTGTGGTAT
184 GTGACCTAGA ATTACAGTCA GATTTTCAGAA AATGATTCTC TCATTTTGCT GATAAGGACT
244 GATTCGTTTT ACTGAGGGAC GGCAGAACTA GTTTCCTATG AGGGCATGGG TGAATACAAC
304 TGAGGCTTCT CATGGGAGGG AATCTCTACT ATCCAAATTT ATTAGGAGAA AATTGAAAAT
364 TTCCAACCTT GTCTCTCTCT TACCTCTGTG TAAGGCAAAT ACCTTATTCT TGTGGTGTTT
424 TTGTAACCTT TTCAAACCTT CATTGATTGA ATGCCTGTTC TGGCAATACA TTAGGTTGGG
484 CACATAAGGA ATACCAACAT AAATAAAACA TTCTAAAAGA AGTTTACGAT CTAATAAAGG
544 AGACAGGTAC ATAGCAAACCT AATTCAAAGG AGCTAGAAGA TGGAGAAAAT CCTGAATGTG
604 GACTAAGTCA TTCAACAAAG TTTTCAGGAA GCACAAAGAG GAGGGGCTCC CCTCACAGAT
664 ATCTGGATTA GAGGCTGGCT GAGCTGATGG TGGCTGGTGT TCTCTGTTGC AGAAGTCAAG
724 ATGGCCAAAG TTCCAGACAT GTTTGAAGAC CTGAAGAACT GTTACAGGTA AGGAATAAGA
784 TTTATCTCTT GTGATTTAAT GAGGGTTTCA AGGCTCACCA GAATCCAGCT AGGCATAACA
844 GTGGCCAGCA TGGGGGCAGG CCGGCAGAGG TTGTAGAGAT GTGTACTAGT CCTGAAGTCA
904 GAGCAGGTTT AGAGAAGACC CAGAAAAACT AAGCATTCAG CATGTTAAAC TGAGATTACA
964 TTGGCAGGGA GACCGCCATT TTAGAAAAAT TATTTTGTAG GTCTGCTGAG CCCTACATGA
1024 ATATCAGCAT CAACCTTAGAC ACAGCCTCTG TTGAGATCAC ATGCCCTGAT ATAAGAATGG
1084 GTTTTACTGG TCCATTCTCA GGAAAACCTT ATCTCATTCA GGAACAGGAA ATGGCTCCAC
1144 AGCAAGCTGG GCATGTGAAC TCACATATGC AGGCAAATCT CACTCAGATG TAGAAGAAAG
1204 GTAAATGAAC ACAAAGATAA AATTACGGAA CATATTAAAC TAACATGATG TTTCCATTAT
1264 CTGTAGTAAA TACTAACACA AACTAGGCTG TCAAAATTTT GCCTGGATAT TTTACTAAGT
1324 ATAAATTATG AAATCTGTTT TAGTGAATAC ATGAAAGTAA TGTGTAACAT ATAAT CTATT
1384 TGGTTAAAT AAAAAGGAAG TGCTTCAAAA CCTTTCTTTT CTCTAAAGGA GCTTAACATT
1444 CTTCCCTGAA CTTCAATTAA AGCTCTTCAA TTTGTTAGCC AAGTCCAATT TTTACAGATA
1504 AAGCACAGGT AAAGCTCAAA GCCTGTCTTG ATGACTACTA ATTCCAGATT AGTAAGATAT

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1564	GAATTACTCT	ACCTATGTGT	ATGTGTAGAA	GTCCTTAAAT	TTCAAAGATG	ACAGTAATGG
1624	CCATGTGTAT	GTGTGTGACC	CACAACTATC	ATGGTCATTA	AAGTACATTG	GCCAGAGACC
1684	ACATGAAATA	ACAACAATTA	CATTCTCATC	ATCTTATTTT	GACAGTGAAA	ATGAAGAAGA
1744	CAGTTCCTCC	ATTGATCATC	TGTCTCTGAA	TCAGGTAAGC	AAATGACTGT	AATTCTCATG
1804	GGACTGCTAT	TCTTACACAG	TGGTTTCTTC	ATCCAAAGAG	AACAGCAATG	ACTTGAATCT
1864	TAAATACTTT	TGTTTTACCC	TCCTAGAGA	TCCAGAGACC	TGTCTTTCAT	TATAAGTGAG
1924	ACCAGCTGCC	TCTCTAAACT	AATAGTTGAT	GTGCATTGGC	TTCTCCCAGA	ACAGAGCAGA
1984	ACTATCCCAA	ATCCCTGAGA	ACTGGAGTCT	CCTGGGGCAG	GCTTCATCAG	GATGTTAGTT
2044	ATGCCATCCT	GAGAAAGCCC	CGCAGGCCGC	TTCAACAGGT	GTCTGTCTCC	TAACGTGATG
2104	TGTTGTGGTT	GTCTTCTCTG	ACACCAGCAT	CAGAGGTTAG	AGAAAGTCTC	CAAACATGAA
2164	GCTGAGAGAG	AGGAAGCAAG	CCAGCTGAAA	GTGAGAAGTC	TACAGCCACT	CATCAATCTG
2224	TGTTATTGTG	TTTGGAGACC	ACAAATAGAC	ACTATAAGTA	CTGCCTAGTA	TGTCTTCAGT
2284	ACTGGCTTTA	AAAGCTGTCC	CCAAAGGAGT	ATTTCTAAAA	TATTTTGAGC	ATTGTTAAGC
2344	AGATTTTTTA	CCTCCTGAGA	GGGAACTAAT	TGGAAAGCTA	CCACTCACTA	CAATCATGTG
2404	TAACCTATTT	AGTTACAACA	TCTCATTTTT	GAGCATGCAA	ATAAATGAAA	AAGTCTTCCT
2464	AAAAAAATCA	TCTTTTTTATC	CTGGAAGGAG	GAAGGAAGGT	GAGACAAAAG	GGAGAGAGGG
2524	AGGGAAGCCT	AATGAAACAC	CAGTTACCTA	AGACCAGAAT	GGAGATCCTC	CTCACTACCT
2584	CTGTTGAATA	CAGCACCTAC	TGAAAGAACT	TTCATTCCCT	GACCATGAAC	AGCCTCTCAG
2644	CTTCTGTTTT	CCTTCCTCAC	AGAAATCCTT	CTATCATGTA	AGCTATGGCC	CACTCCATGA
2704	AGGCTGCATG	GATCAATCTG	TGTCTCTGAG	TATCTCTGAA	ACCTCTAAAA	CATCCAAGCT
2764	TACCTTCAAG	GAGAGCATGG	TGGTAGTAGC	AACCAACGGG	AAGGTTCTGA	AGAAGAGACG
2824	GTTGAGTTTA	AGCCAATCCA	TCATCATGTA	TGACCTGGAG	GCCATCGCCA	ATGACTCAGA
2884	GGAAGGTAAG	GGGTCAAGCA	CAATAATATC	TTTCTTTTAC	AGTTTTAAGC	AAGTAGGGAC
2944	AGTAGAATTT	AGGGGAAAAT	TAAACGTGGA	TTCAGAATAA	CAAGAAGACA	ACCAAGCATT
3004	AGTCTGGTAA	CTATACAGAG	GAAAATTAAT	TTTTATCCTT	CTCCAGGAGG	GAGAAATGAG
3064	CAGTGGCCTG	AATCGAGAAT	ACTTGCTCAC	AGCCATTATT	TCTTAGCCAT	ATTGTAAAGG
3124	TCGTGTGACT	TTTAGCCTTT	CAGGAGAAAG	CAGTAATAAG	ACCACTTACG	AGCTATGTTT
3184	CTCTCATACT	AACATATGCC	CCTTGGTCAT	GTTACATAAT	CTTTTTCGTG	TTCAGTTTCC
3244	TCTACTGTAA	AATGGGAGATA	ATCAGAATCC	CCCACTCATT	GGATTGTTGT	AAAGATTAAAG
3304	AGTCTCAGGC	TTTACAGACT	GAGCTAGCTG	GGCCCTCCTG	ACTGTTATAA	AGATTAAATG
3364	AGTCAACATC	CCCTAACTTC	TGGACTAGAA	TAATGTCTGG	TACAAAGTAA	GCACCCAATA
3424	AATGTTAGTG	ATTACTATCA	TTATTATTAT	TATTTTATTT	TTTTTTTTTG	AGATGGAGTC
3484	TGGCTCTGTC	ACCCAGGCTG	GAGTGCAGTG	GCACAATCTC	GGCTCACTGC	AAGCTCTGCC
3544	TCCTGGGTTT	ATGCCATTCT	CCTGCCTCAG	CCTCCCGAGT	AAGCTGGGAA	TACAGGCACC
3604	CGCCACTGTT	CCCGGCTAAT	TTTTTGATTT	TTTAGTAGAG	ACGGAGTTTC	ACCGTGGTCT
3664	CCATCTCCTC	GTGATCCACC	CACCTTGGCC	TCCCAAAGTG	CCGGGATTAC	AGGCGTGAGC
3724	CACCGCGCCC	GGCCTATTAT	TATTATTATT	ACTACTACTA	CTACCTATAT	GAATACTACC
3784	AGCAATACTA	ATTTATTAAT	GACTGGATTA	TGTCTAAACC	TCACAAGAAT	CCTACCTTCT
3844	CATTTTACAT	AAAAGGAAAC	TAAGCTCATT	GAGATAGGTA	AACTGCCCAA	TGGCATACAT
3904	CTGTAAGTGG	GAGAGCCTCA	AATCTAATTC	AGTTCTACCT	GAGTAAAAAA	ATCATGGTTT
3964	CTCCTCCATC	CCTTTACTGT	ACAAGCCTCC	ACATGAACTA	TAAACCCAA	ATTCCTGTTT
4024	TTAAGATAAT	ACCTAAGCAA	TAACGCATGT	TCACCTAGAA	GGTTTTAAAA	TGTAAACAAA
4084	TATAAGAAAA	TAAAAATCAC	TCATATCGTC	AGTGAGAGTT	TACTACTGCC	AGCACTATGG
4144	TATGTTTCCT	TAAAATCTTT	GCTATACACA	TACCTACATG	TGAACAAATA	TGTCTAACAT
4204	CAAGACCACA	CTATTTACAA	CTTTATATCC	AGCTTTTCTT	ACTTAGCAAT	GTATTGAGGA
4264	CATTTTAGAG	TGCCCCGTTT	TCACCATTAT	AAGCAATGCA	ACAATGAACA	TCTGTATAAA
4324	TAAATATTCA	TTTCTCTCAC	CCTTTATTTT	CTTAGAATAT	ATTCCTAGAA	GTAGAATTTT
4384	CCAGAGCCAT	GAGGATTTGT	GACGCTATTG	ATATGTGCCA	CTTTGCACTC	TCTGTGACAT
4444	ATATAATTAT	TTTTAATGCA	TTCATTTTTT	TCTCAGAGTG	CATTTCGTTT	AAAACATAGA
4504	CGGGAAATAC	TGGTAGTCTT	CCTTGTCAGT	TAGAAACACC	CAAACAATGA	AAAATGAAAA
4564	AGTTGCACAA	ATAGTCTCTA	AAAACAATGA	AACTATTGCC	TGAGGAATTG	AAGTTTAAAA
4624	AGAAGCACAT	AAGCAACAAC	AAGGATAATC	CTAGAAAACC	AGTTCTGCTG	ACTGGGTGAT
4684	TTCACTTCTC	TTTGCTTCCT	CATCTGGATT	GGAATATTCC	TAATACCCCC	TCCAGAATA

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4744 TTTTCCCTGT TTGTA TAGA CTGTGTATAT CATCTGTGTT TGTACATAGA CATTAAATCTG
4804 CACTTGTGAT CATGGTTTTA GAAATCATCA AGCCTAGGTC ATCACCTTTT AGCTTCCTGA
4864 GCAATGTGAA ATACAACTTT ATGAGGATCA TCAAATACGA ATTCATCCTG AATGACGCCC
4924 TCAATCAAAG TATAATTCGA GCCAATGATC AGTACCTCAC GGCTGCTGCA TTACATAATC
4984 TGGATGAAGC AGGTACATTA AAATGGCACC AGACATTTCT GTCATCCTCC CCTCCTTTCA
5044 TTTACTTATT TATTTATTTT AATCTTTCTG CTTGCAAAAA ACATACCTCT TCAGAGTTCT
5104 GGTTGCACA ATTCTTCCAG AATAGCTTGA AGCACAGCAC CCCATAAAAA ATCCCAAGCC
5164 AGGGCAGAAG GTTCAACTAA ATCTGGAAGT TCCACAAGAG AGAAGTTTCC TATCTTTGAG
5224 AGTAAAGGGT TGTGCACAAA GCTAGCTGAT GTACTACCTC TTTGGTTCTT TCAGACATTC
5284 TTACCCTCAA TTTTAAAACT GAGGAACTG TCAGACATAT TAAATGATTT ACTCAGATTT
5344 ACCCAGAAGC CAATGAAGAA CAATCACTCT CCTTTAAAAA GTCTGTTGAT CAAACTCACA
5404 AGTAACACCA AACCAGGAAG ATCTTTATTA TCTCTGATAA CATATTTGTG AGGCAAAACC
5464 TCCAATAAGC TACAAATATG GCTTAAAGGA TGAAGTTTAG TGTCCAAAAA CTTTTATCAC
5524 ACACATCCAA TTTTCATGGC GGACATGTTT TAGTTTCAAC AGTATACATA TTTTCAAAGG
5584 TCCAGAGAGG CAATTTTGCA ATAAACAAGC AAGACTTTTT CTGATTGGAT GCACTTCAGC
5644 TAACATGCTT TCAACTCTAC ATTTACAAAT TATTTTGTGT TCTATTTTTC TACTTAATAT
5704 TATTTCTGCA ATTTTCCCAA TATTGACATC GTGTATGTAT TTGCCATTTT TAATATCACT
5764 AGACAATTCA ATCAGGTTGC TACGTTGGTC CCTTGGGTTT ACTCTAAATA GCTTGATTGC
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5884 CAAAGAGGAA TGCCTAGATC AATGGGCACA AATAATTTGA CAGCTCTTAT TAAACATTAT
5944 TCTGTAAGTA AAAACTGAAC TACTTTTCAG TATCACTAGC AACATATGAG TGTATCAGCT
6004 TCCTAAACCC CTCCATGTTA GGTCAATTATG AACTTATGAT CTAACAAATT ACAGGTCTT
6064 ATCCCACTAA TGAAATTATA AGAGATTCAA CACTTATTCA GCCCCGAAGG ATTCATTCAA
6124 CGTAGAAAAT TCTAAGAACA TTAACCAAGT ATTTACCTGC CTAGTGAGTG TGAAGACAT
6184 TGTGAAGGAC ACAAAGATGT ATAGAATTCC ATTCCTGACT TCCAGGTATT TACACCATAG
6244 GTGGGGACCT AACTACACAC ACACACACAC ACACACACAC ACCATGCACA
6304 CACAATCTAC ATCAACACTT GATTTTATAC AAATACAATG AATTTACTTT CTTTTTGGTT
6364 CTTCTCTTCA CCAGTGAAAT TTGACATGGG TGCTTATAAG TCATCAAAGG ATGATGCTAA
6424 AATTACCGTG ATTCTAAGAA TCTCAAAAAC TCAATTGTAT GTGACTGCCC AAGATGAAGA
6484 CCAACCAGTG CTGCTGAAGG TCAGTTGTCC TTTGTCTCCA ACTTACCTTC ATTTACATCT
6544 CATATGTTTG TAAATAAGCC CAATAGGCAG ACACCTCTAA CAAGGTGACA CTGTCCTCTT
6604 TCCTTCCTAC CACAGCCCCC ACCTACCCAC CCCACTCCCA TTGATTCCAG AGGCGTGCCT
6664 AGGCAGGATC TATGAGAAAA TATAACAGAG AGTAAGAGGA AAATTACCTT CTTTCTTTTT
6724 CCTTTCCTTG CCTGACCTTA TTCACCTCCC ATCCCAGAGC ATCCATTTAT TCCATTGATC
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6964 CTCTGCATTG ATGTCAGCAT TATCCTTCGT CCCAGTCCTG TCTCCACTAC CACTTTCCCC
7024 CTCAAACACA CACACACACA ACAGCCTTAG ATGTTTTCTC CACTGATAAG TAGGTGACTC
7084 AATTTGTAAG TATATAATCC AAGACCTTCT ATTCCCAAGT AGAATTTATG TGCCTGCCTG
7144 TGCTTTTCTA CCTGGATCAA GTGATGTCTA CAGAGTAGGG CAGTAGCTTC ATTCATGAAC
7204 TCATTCAACA AGCATTATTC ACTGAGAGCC TTGTATTTTT CAGGCATAGT GCCAACAGCA
7264 GTGTGGACAG TGGTGCATCA AAGCCTCTAG TCTCATAGAA CTTAGTCTTC TGGAGGATAT
7324 GGAAAACAGA CAACCCAAAC AACCACAAA AGAGCAAGAT GCTGCAAAAA AAAAAAAAT
7384 GAATAGGGTG CTAAGATAGA GAAAAGTGGG AGAGTGCTAT TTAGACAAAG TGGTAAAAAC
7444 AAAGCCCCTT GTGAGATGAG AGCTGCCGAC AGAGGGGGCG GGTGATGGTT GTGGGTTTTT
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7564 GAGGAGGGGG CGGGTCGTGG TTGTGGGTTT TTGGGTAGGA CATTGAGAGG AGGGGGCGGG
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7684 TTTTGGGACA TTCAGAGGAG TCTGAATGCA CCCAGGCCTA CAACTTCAAG ATGGTAAAGG
7744 ACAGCTCCAA GGATCAGAAG AAGCATTCTT GGAAGTGGG CATTGTGAGA AGGAGGAAAA
7804 ATATGCAGAG ACTAGTGCTT GCAGAGCTTG CATTTGGATT TCATTGAGG TACAATGAAA
7864 ACCCATTAAT GGGTTTCACA CAGTGCAATG GCCTGACCTC ACTTATATTT CCTAAAATAG

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7924	AAAACAGATC	AGAAGGAAGG	CAATAGAGAA	GCAGAAAGTC	CAATGAGGAG	GTTTCACAGC
7984	AGTCATGGG	GTGGGGTAAG	GAAAAGAAGT	GGAAAGAAAC	AGACAGAATT	GGGTTATATT
8044	TTGGAGATAG	AACCAACAGA	AGGAAGAGGA	GAAACAACAT	TTACTGAGAA	GGGAAAAAGT
8104	AGGAGAGGAA	TAGGTTTGGG	AAATAAATCC	TGCTGACATT	GGAAACCCCA	AGGAAGCCTC
8164	AAAAGTATAT	TTACTTGCTT	TAGATTTAAA	AGAATAGGAA	AGAAGCATCT	CAACTTGGAA
8224	TTTGAAATCT	ATTTTTCCTT	AAAAGTATTG	TTAAATTCTA	CTCATACTCA	CAAGAAAAGT
8284	ACATTCTAAA	GAGTATATTG	AAAGAGTTTA	CTGATATACT	TAGGAATTTT	GTGTGTATGT
8344	GTGTGTGTGT	ATGTGTGTGT	GTGTGTTTAA	CCTTCAATTG	TTGACTTAAA	TACTGAGATA
8404	AATGTCATCT	AAATGCTAAA	TTGATTTCCC	AAAGGTATGA	TTTGTTCCTT	TGGAGATCAA
8464	AATGTTTAGG	GGGCTTAGAA	TCACTGTAGT	GCTCAGATTT	GATGCAAAAT	GTCTTAGGCC
8524	TATGTTGAAG	GCAGGACAGA	AACAATGTTT	CCCTCCTACC	TGCCTGGATA	CAGTAAGATA
8584	CTAGTGTAC	TGACAATCTT	CATAACTAAT	TTAGATCTCT	CTCCAATCAA	CTAAGGAAAT
8644	CAACTCTTAT	TAATAGACTG	GGCCACACAT	CTACTAGGCA	TGTAATAAAT	GCTTGCTGAA
8704	TGAACAAATG	AATGAAGAGC	CTATAGCATC	ATGTTACAGC	CATAGTCCTA	AAGTGGTGTT
8764	TCTCATGAAG	GCCAAATGCT	AAGGGATTGA	GCTTCAGTCC	TTTTTCTAAC	ATCTTGTCTT
8824	CTAACAGAAT	TCTCTTCTTT	TCTTCATAGG	AGATGCCTGA	GATACCCAAA	ACCATCACAG
8884	GTAGTGAGAC	CAACCTCCTC	TTCTTCTGGG	AAACTCACGG	CACTAAGAAC	TATTTACAT
8944	CAGTTGCCCC	TCCAAACTTG	TTTATTGCCA	CAAAGCAAGA	CTACTGGGTG	TGCTTGGCAG
9004	GGGGGCCACC	CTCTATCACT	GACTTTCAGA	TACTGGAAAA	CCAGGCGTAG	GTCTGGAGTC
9064	TCACTTGTCT	CACCTGTGCA	GTGTTGACAG	TTCATATGTA	CCATGTACAT	GAAGAAGCTA
9124	AATCCTTTAC	TGTTAGTCAT	TTGCTGAGCA	TGTACTGAGC	CTTGTAATTC	TAAATGAATG
9184	TTTACACTCT	TTGTAAGAGT	GGAACCAACA	CTAACATATA	ATGTTGTTAT	TTAAGAACA
9244	CCCTATATTT	TGCATAGTAC	CAATCATTTT	AATTATTATT	CTTCATAACA	ATTTTAGGAG
9304	GACCAGAGCT	ACTGACTATG	GCTACCAAAA	AGACTCTACC	CATATTACAG	ATGGGCAAAAT
9364	TAAGGCATAA	GAAAACTAAG	AAATATGCAC	AATAGCAGTT	GAAACAAGAA	GCCACAGACC
9424	TAGGATTTCA	TGATTTTCATT	TCAACTGTTT	GCCTTCTGCT	TTTAAGTTGC	TGATGAACCTC
9484	TTAATCAAAT	AGCATAAGTT	TCTGGGACCT	CAGTTTTATC	ATTTTCAAAA	TGGAGGGAAT
9544	AATACCTAAG	CCTTCCTGCC	GCAACAGTTT	TTTATGCTAA	TCAGGGAGGT	CATTTTGGTA
9604	AAATACTTCT	CGAAGCCGAG	CCTCAAGATG	AAGGCAAAGC	ACGAAATGTT	ATTTTTTAAT
9664	TATTATTTAT	ATATGTATTT	ATAAATATAT	TTAAGATAAT	TATAATATAC	TATATTTATG
9724	GGAACCCCTT	CATCCTCTGA	GTGTGACCAG	GCATCCTCCA	CAATAGCAGA	CAGTGTTTTC
9784	TGGGATAAGT	AAGTTTGATT	TCATTAATAC	AGGGCATTTT	GGTCCAAGTT	GTGCTTATCC
9844	CATAGCCAGG	AAACTCTGCA	TTCTAGTACT	TGGGAGACCT	GTAATCATAT	AATAAATGTA
9904	CATTAATTAC	CTTGAGCCAG	TAATTGGTCC	GATCTTTGAC	TCTTTTGCCA	TTAAACTTAC
9964	CTGGGCATTC	TTGTTTCATT	CAATTCCACC	TGCAATCAAG	TCCTACAAGC	TAAAATTAGA
10024	TGAACTCAAC	TTTGACAACC	ATGAGACCAC	TGTTATCAAA	ACTTTCTTTT	CTGGAATGTA
10084	ATCAATGTTT	CTTCTAGGTT	CTAAAAATTG	TGATCAGACC	ATAATGTTAC	ATTATTATCA
10144	ACAATAGTGA	TTGATAGAGT	GTTATCAGTC	ATAACTAAAT	AAAGCTTGCA	ACAAAATTCT
10204	CTGACACATA	GTTATTCATT	GCCTTAATCA	TTATTTTACT	GCATGGTAAT	TAGGGACAAA
10264	TGGTAAATGT	TTACATAAAT	AATTGTATTT	AGTGTACTT	TATAAAATCA	AACCAAGATT
10324	TTATATTTT	TTCTCCTCTT	TGTTAGCTGC	CAGTATGCAT	AAATGGCATT	AAGAATGATA
10384	ATATTTCCGG	GTTCACTTAA	AGCTCATATT	ACACATACAC	AAAACATGTG	TTCCCATCTT
10444	TATACAAACT	CACACATACA	GAGCTACATT	AAAAACAAC	AATAGGCCAG	GCACGGTGGC
10504	TCAGACCTGT	AATCCCAGCA	CTTTGGGAGG			

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Figure 2. DNA Sequence of the human IL-1B gene. (GenBank Accession No. X04500)

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-1933 AGAAAGAAAG AGAGAGAGAA AGAAAAGAAA GAGGAAGGAA GGAAGGAAGG AAGAAAGACA
-1873 GGCTCTGAGG AAGGTGGCAG TTCCTACAAC GGGAGAACCA GTGGTTAATT TGCAAAGTGG
-1813 ATCCTGTGGA GGCANNCAGA GGAGTCCCCT AGGCCACCCA GACAGGGCTT TTAGCTATCT
-1753 GCAGGCCAGA CACCAAATTT CAGGAGGGCT CAGTGTTAGG AATGGATTAT GGCTTATCAA
-1693 ATTCACAGGA AACTAACATG TTGAACAGCT TTTAGATTTT CTGTGGAAAA TATAACTTAC
-1633 TAAAGATGGA GTTCTTGTGA CTGACTCCTG ATATCAAGAT ACTGGGAGCC AAATTAAAAA
-1573 TCAGAAGGCT GCTTGGAGAG CAAGTCCATG AAATGCTCTT TTTCCACAG TAGAACCTAT
-1513 TTCCCTCGTG TCTCAAATAC TTGCACAGAG GCTCACTCCC TTGGATAATG CAGAGCGAGC
-1453 ACGATACCTG GCACATACTA ATTTGAATAA AATGCTGTCA AATTCCCATT CACCCATTCA
-1393 AGCAGCAAAC TCTATCTCAC CTGAATGTAC ATGCCAGGCA CTGTGCTAGA CTTGGCTCAA
-1333 AAAGATTTCA GTTTCCTGGA GGAACCAGGA GGGCAAGGTT TCAACTCAGT GCTATAAGAA
-1273 GTGTTACAGG CTGGACACGG TGGCTCACGC CTGTAATCCC AACATTTGGG AGGCCGAGGC
-1213 GGGCAGATCA CAAGGTCAGG AGATCGAGAC CATCCTGGCT AACATGGTGA AACCCGTGTCT
-1153 CTAATAAAAA TACAAAAAAT TAGCCGGGCG TTGGCGGCAG GTGCCTGTAG TCCCAGCTGC
-1093 TGGGGAGGCT GAGGCAGGAG AATGGTGTGA ACCCGGGAGG CGGAACCTGC AGGGGGCCGA
-1033 GATCGTGCCA CTGCACTCCA GCCTGGGCGA CAGAGTGAGA CTCTGTCTCA AAAAAAAAAA
-973 AAAAGTGTTA TGATGCAGAC CTGTCAAAGA GGCAAAGGAG GGTGTTCCCTA CACTCCAGGC
-913 ACTGTTCTA ACCTGGACTC TCATTTCATT TACAAATGGA GGGCTCCCCT GGGCAGATCC
-853 CTGGAGCAGG CACTTTGCTG GTGTCTCGGT TAAAGAGAAA CTGATAACTC TTGGTATTAC
-793 CAAGAGATAG AGTCTCAGAT GGATATTCTT ACAGAAACAA TATCCCCTT TTTTCAGATT
-733 CACCAAAAAA TCATTTTAGG CAGAGCTCAT CTGGCATTGA TCTGGTTTCT CCATGAGATT
-673 GGCTAGGGTA ACAGCACCTG GTCTTGCAGG GTTGTGTGAG CTTATCTCCA GGGTTGCCCC
-613 AACTCCGTCA GGAGCCTGAA CCCTGCATAC CGTATGTTCT CTGCCCCAGC CAAGAAAGGT
-553 CAATTTTCTC CTCAGAGGCT CCTGCAATTG ACAGAGAGCT CCCGAGGCAG AGAACAGCAC
-493 CCAAGGTAGA GACCCACACC CTCAATACAG ACAGGGAGGG CTATTGGCCC TTCATTGTAC
-433 CCATTTATCC ATCTGTAAGT GGGAAAGATC CTAAACTTAA GTACAAAGAA GTGAATGAAG
-373 AAAAGTATGT GCATGTATAA ATCTGTGTGT CTTCCACTTT GTCCACATA TACTAAATTT
-313 AAACATTCTT CTAACGTGGG AAAATCCAGT ATTTTAATGT GGACATCAAC TGCACAACGA
-253 TTGTCAGGAA AACAAATGCAT ATTTGCATGG TGATACATTT GCAAATGTG TCATAGTTTG
-193 CTACTCCTTG CCCTTCCATG AACCAGGAAA TTATCTCAGT TTATTAGTCC CCTCCCCTAA
-133 GAAGCTTCCA CCAATACTCT TTTCCCCTTT CTTTAACTT GATTGTGAAA TCAGGTATTC
-73 AACAGAGAAA TTTCTCAGCC TCCTACTTCT GCTTTTGAAA GCTATAAAAA CACGGAGGGA
-13 GAAACTGGCA GATACCAAAC CTCTTCGAGG CACAAGGCAC AACAGGCTGC TCTGGATTCT
48 TCTTCAGCCA ATCTTCATTG CTCAAGTATG ACTTTAATCT TCCTTACAAC TAGGTGCTAA
108 GGGAGTCTCT CTGTCTCTCT GCCTCTTTGT GTGTATGCAT ATTCTCTCTC TCTCTCTCTT
168 TCTTTCTCTG TCTCTCCTCT CCTTCCTCTC TGCTCCTCT CTCAGCTTTT TGCAAAAATG
228 CCAGGTGTAA TATAATGCTT ATGACTCGGG AAATATTCTG GGAATGGATA CTGCTTATCT
288 AACAGCTGAC ACCCTAAAGG TTAGTGTCAA AGCCTCTGCT CCAGCTCTCC TAGCCAATAC
238 ATTGCTAGTT GGGGTTTGGT TTAGCAAATG CTTTCTCTA GACCCAAAGG ACTTCTCTTT
308 CACACATTCA TTCATTTACT CAGAGATCAT TTCTTTGCAT GACTGCCATG CACTGGATGC
468 TGAGAGAAAT CACACATGAA CGTAGCCGTC ATGGGGAAGT CACTCATTTT CTCCTTTTTA
528 CACAGGTGTC TGAAGCAGCC ATGGCAGAAG TACCTGAGCT CGCCAGTGAA ATGATGGCTT
588 ATTACAGGTC AGTGGAGACG CTGAGACCAG TAACATGAGC AGGTCTCTCT TTTCAAGAGT
648 AGATGTTTAT CTGTGCTTGG AGACCAGATT TTTCCCCTAA ATTGCCTCTT TCAGTGGCAA
708 ACAGGGTGCC AAGTAAATCT GATTTAAAGA CTACTTTCCC ATTACAAGTC CCTCCAGCCT
768 TGGGACCTGG AGGCTATCCA GATGTGTTGT TGCAAGGGCT TCCTGCAGAG GCAAATGGGG
828 AGAAAAGATT CCAAGCCAC AATACAAGGA ATCCCTTTGC AAAGTGTGGC TTGGAGGGAG
888 AGGGAGAGCT CAGATTTTAG CTGACTCTGC TGGGCTAGAG GTTAGGCCTC AAGATCCAAC
948 AGGGAGCACC AGGGTGCCCA CCTGCCAGGC CTAGAATCTG CCTTCTGGAC TGTCTGCGC
1008 ATATCACTGT GAAACTTGCC AGGTGTTTCA GGCAGCTTTG AGAGGCAGGC TGTTTGCAGT

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1068	TTCTTATGAA	CAGTCAAGTC	TTGTACACAG	GGAAGGAAAA	ATAAACCTGT	TTAGAAGACA
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1188	CTGATGGCCC	TAAACAGATG	AAGGTAAGAC	TATGGGTTTA	ACTCCCAACC	CAAGGAAGGG
1248	CTCTAACACA	GGGAAAGCTC	AAAGAAGGGA	GTTCTGGGCC	ACTTTGATGC	CATGGTATTT
1308	TGTTTTAGAA	AGACTTTAAC	CTCTTCCAGT	GAGACACAGG	CTGCACCACT	TGCTGACCTG
1368	GCCACTTGGT	CATCATATCA	CCACAGTCAC	TCACTAACGT	TGGTGGTGGT	GGCCACACTT
1428	GGTGGTGACA	GGGGAGGAGT	AGTGATAATG	TTCCCATTTT	ATAGTAGGAA	GACAACCAAG
1488	TCTTCAACAT	AAATTTGATT	ATCCTTTTAA	GAGATGGATT	CAGCCTATGC	CAATCACTTG
1548	AGTTAAACTC	TGAAACCAAG	AGATGATCTT	GAGAACTAAC	ATATGTCTAC	CCCTTTTGAG
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1668	CAAAAAGATG	AATTGAGACT	TGAAAGAAAA	CCATTCACTT	GCTGTTTGAC	CTTGACAAGT
1728	CATTTTACCC	GCTTTGGACC	TCATCTGAAA	AATAAAGGGC	TGAGCTGGAT	GATCTCTGAG
1788	ATTCCAGCAT	CCTGCAACCT	CCAGTTCTGA	AATATTTTCA	GTTGTAGCTA	AGGGCATTTG
1848	GGCAGCAAAT	GGTCATTTTT	CAGACTCATC	CTTACAAAGA	GCCATGTTAT	ATTCCTGCTG
1908	TCCCTTCTGT	TTTATATGAT	GCTCAGTAGC	CTTCCTAGGT	GCCCAGCCAT	CAGCCTAGCT
1968	AGGTCAGTTG	TGCAGGTTGG	AGGCAGCCAC	TTTTCTCTGG	CTTTATTTTA	TTCCAGTTTG
2028	TGATAGCCTC	CCCTAGCCTC	ATAATCCAGT	CCTCAATCTT	GTTAAAAACA	TATTTCTTTA
2088	GAAGTTTAA	GACTGGCATA	ACTTCTTGCC	TGCAGCTGTG	GGAGGAGCCC	ATTGGCTTGT
2148	CTGCCTGGCC	TTTGCCCCCC	ATTGCCCTCT	CCAGCAGCTT	GGCTCTGCTC	CAGGCAGGAA
2208	ATTCTCTCCT	GCTCAACTTT	CTTTTGTGCA	CTTACAGGTC	TCTTTAACTG	TCTTTCAAGC
2268	CTTTGAACCA	TTATCAGCCT	TAAGGCAACC	TCAGTGAAGC	CTAATACGG	AGCTTCTCTG
2328	AATAAGAGGA	AAGTGGAAC	ATTTACAAAA	AAGTACTCTC	ACAGGATTTG	CAGAATGCCT
2388	ATGAGACAGT	GTTATGAAAA	AGGAAAAAAA	AGAACAGTGT	AGAAAAATTG	AATACTTGCT
2448	GAGTGAGCAT	AGGTGAATGG	AAAATGTTAT	GGTCATCTGC	ATGAAAAAGC	AAATCATAGT
2508	GTGACAGCAT	TAGGGATACA	AAAAGATATA	GAGAAGGTAT	ACATGTATGG	TGTAGGTGGG
2568	GCATGTACAA	AAAGATGACA	AGTAGAATCG	GGATTTATTC	TAAAGAATAG	CCTGTAAGGT
2628	GTCCAGAAGC	CACATTCTAG	TCTTGAGTCT	GCCTCTACCT	GCTGTGTGCC	CTTGAGTACA
2688	CCCTTAACCT	CCTTGAGCTT	CAGAGAGGGA	TAATCTTTTT	ATTTTATTTT	ATTTTATTTT
2748	GTTTTGTTTT	GTTTTGTTTT	GTTTTATGAG	ACAGAGTCTC	ACTCTGTTGC	CCAGGCTGGA
2808	GTGCAGTGGT	ACAATCTTGG	CTTACTGCAT	CCTCCACCTC	CTGAGTTCAA	GCGATTCTCC
2868	TTCCTCAGTC	TCCTGAATAG	CTAGGATTAC	AGGTGCACCC	CACCACACCC	AGCTAATTTT
2928	TGTATTTTTTA	GTAGAGAAGG	GGTTTCGCCA	TGTTGGCCAG	GCTGGTTTTG	AAGTCCTGAC
2988	CTAAATGATT	CATCCACCTC	GGCTTCCCAA	AGTGCTGGGA	TTACAGGCAT	GAGCCACCAC
3048	GCCTGGCCCA	GAGAGGGATG	ATCTTTAGAA	GCTCGGGATT	CTTCAAGCC	CTTTCCTCCT
3108	CTCTGAGCTT	TCTACTCTCT	GATGTCAAAG	CATGGTTCCCT	GGCAGGACCA	CCTCACCAGG
3168	CTCCCTCCCT	CGCTCTCTCC	GCAGTGCTCC	TTCCAGGACC	TGGACCTCTG	CCCTCTGGAT
3228	GGCGGCATCC	AGCTACGAAT	CTCCGACCAC	CACTACAGCA	AGGGCTTCAG	GCAGGCCGCG
3288	TCAGTTGTTG	TGGCCATGGA	CAAGCTGAGG	AAGATGCTGG	TTCCCTGCCC	ACAGACCTTC
3348	CAGGAGAATG	ACCTGAGCAC	CTTCTTTCCC	TTCATCTTTG	AAGAAGGTAG	TTAGCCAAGA
3408	GCAGGCAGTA	GATCTCCACT	TGTGTCCCTCT	TGGAAGTCAT	CAAGCCCCAG	CCAACTCAAT
3468	TCCCCCAGAG	CCAAAGCCCT	TTAAAGGTAG	AAGGCCCAGC	GGGGAGACAA	AACAAAGAAG
3528	GCTGGAAACC	AAAGCAATCA	TCTCTTTAGT	GGAAACTATT	CTTAAAGAAG	ATCTTGATGG
3588	CTACTGACAT	TTGCAACTCC	CTCACTCTTT	CTCAGGGGCC	TTTCACTTAC	ATTGTCACCA
3648	GAGGTTTCGT	ACCTCCCTGT	GGGCTAGTGT	TATGACCATC	ACCATTTTAC	CTAAGTAGCT
3708	CTGTTGCTCG	GCCACAGTGA	GCAGTAATAG	ACCTGAAGCT	GGAACCCATG	TCTAATAGTG
3768	TCAGGTCCAG	TGTTCTTAGC	ACCCCCACTC	CCAGCTTCAT	CCCTACTGGT	GTTGTCATCA
3828	GACTTTGACC	GTATATGCTC	AGGTGTCCTC	CAAGAAATCA	AATTTTGCCA	CCTCGCCTCA
3888	CGAGGCCTGC	CCTTCTGATT	TTATACCTAA	ACAACATGTG	CTCCACATTT	CAGAACCCTAT
3948	CTTCTTCGAC	ACATGGGATA	ACGAGGCTTA	TGTGCACGAT	GCACCTGTAC	GATCACTGAA
4008	CTGCACGCTC	CGGGACTCAC	AGCAAAAAAG	CTTGGTGATG	TCTGGTCCAT	ATGAACTGAA
4068	AGCTCTCCAC	CTCCAGGGAC	AGGATATGGA	GCAACAAGGT	AAATGGAAAC	ATCCTGGTTT
4128	CCCTGCCTGG	CCTCCTGGCA	GCTTGCTAAT	TCTCCATGTT	TTAAACAAAG	TAGAAAGTTA
4188	ATTTAAGGCA	AATGATCAAC	ACAAGTGAAA	AAAAATATTA	AAAAGGAATA	TACAACTTTT

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4248	GGTCCTAGAA	ATGGCACATT	TGATTGCACT	GGCCAGTGCA	TTTGTTAACA	GGAGTGTGAC
4308	CCTGAGAAAT	TAGACGGCTC	AAGCACTCCC	AGGACCATGT	CCACCCAAGT	CTCTTGGGCA
4368	TAGTGCAGTG	TCAATTCTTC	CACAATATGG	GGTCATTTGA	TGGACATGGC	CTAACTGCCT
4428	GTGGGTCTCT	TCTTCCTGTT	GTTGAGGCTG	AAACAAGAGT	GCTGGAGCGA	TAATGTGTCC
4488	ATCCCCCTCC	CCAGTCTTCC	CCCCTTGCCC	CAACATCCGT	CCCACCCAAT	GCCAGGTGGT
4548	TCCTTGTAGG	GAAATTTTAC	CGCCCAGCAG	GAACCTATAT	CTCTCCGCTG	TAACGGGCAA
4608	AAGTTTCAAG	TGCGGTGAAC	CCATCATTAG	CTGTGGTGAT	CTGCCTGGCA	TCGTGCCACA
4668	GTAGCCAAAG	CCTCTGCACA	GGAGTGTGGG	CAACTAAGGC	TGCTGACTTT	GAAGGACAGC
4728	CTCACTCAGG	GGGAAGCTAT	TTGCTCTCAG	CCAGGCCAAG	AAAATCCTGT	TTCTTTGGAA
4788	TCGGGTAGTA	AGAGTGATCC	CAGGGCCTCC	AATTGACACT	GCTGTGACTG	AGGAAGATCA
4848	AAATGAGTGT	CTCTCTTTGG	AGCCACTTTC	CCAGCTCAGC	CTCTCCTCTC	CCAGTTTCTT
4908	CCCATGGGCT	ACTCTCTGTT	CCTGAAACAG	TTCTGGTGCC	TGATTTCTGG	CAGAAGTACA
4968	GCTTCACCTC	TTTCCTTTCC	TTCCACATTG	ATCAAGTTGT	TCCGCTCCTG	TGGATGGGCA
5028	CATTGCCAGC	CAGTGACACA	ATGGCTTCCT	TCCTTCCTTC	CTTCAGCATT	TAAAATGTAG
5088	ACCCTCTTTC	ATTCTCCGTT	CCTACTGCTA	TGAGGCTCTG	AGAAACCCCT	AGGCCTTTGA
5148	GGGGAAACCC	TAAATCAACA	AAATGACCCCT	GCTATTGTCT	GTGAGAAGTC	AAGTTATCCT
5208	GTGTCTTAGG	CCAAGGAACC	TCACTGTGGG	TTCCCACAGA	GGCTACCAAT	TACATGTATC
5268	CTACTCTCGG	GGCTAGGGGT	TGGGGTGACC	CTGCATGCTG	TGTCCCTAAC	CACAAGACCC
5328	CCTTCTTTCT	TCAGTGGTGT	TCTCCATGTC	CTTTGTACAA	GGAGAAGAAA	GTAATGACAA
5388	AATACCTGTG	GCCTTGGGCC	TCAAGGAAAA	GAATCTGTAC	CTGTCTGCG	GTTTGAAGA
5448	TGATAAGCCC	ACTCTACAGC	TGGAGGTAAG	TGAATGCTAT	GGAATGAAGC	CCTTCTCAGC
5508	CTCCTGCTAC	CACTTATTCC	CAGACAATTC	ACCTTCTCCC	CGCCCCCATC	CCTAGGAAAA
5568	GCTGGGAACA	GGTCTATTTG	ACAAGTTTTG	CATTAATGTA	AATAAATTTA	ACATAATTTT
5628	TAAGTGCCTG	CAACCTTCAA	TCCTGCTGCA	GAAAATTTAA	TCATTTTGCC	GATGTTATTA
5688	TGTCTTACCA	TAGTTACAAC	CCCAACAGAT	TATATATTGT	TAGGGCTGCT	CTCATTTGAT
5748	AGACACCTTG	GGAAATAGAT	GACTTAAAGG	GTCCCATTAT	CACGTCCACT	CCACTCCCAA
5808	AATCACCACC	ACTATCACCT	CCAGCTTTCT	CAGCAAAAGC	TTCATTTCCA	AGTTGATGTC
5868	ATTCTAGGAC	CATAAGGAAA	AATACAATAA	AAAGCCCCTG	GAACTAGGT	ACTTCAAGAA
5928	GCTCTAGCTT	AATTTTCACC	CCCCCAAAAA	AAAAAAATTC	TCACCTACAT	TATGCTCCTC
5988	AGCATTGGGC	ACTAAGTTTT	AGAAAAGAAG	AAGGGCTCTT	TTAATAATCA	CACAGAAAGT
6048	TGGGGGCCCA	GTTACAACCT	AGGAGTCTGG	CTCCTGATCA	TGTGACCTGC	TCGTCACTTT
6108	CCTTTCTGGC	CAACCCAAAG	AACATCTTTC	CCATAGGCAT	CTTTGTCCCT	TGCCCCACAA
6168	AAATTCTTCT	TTCTCTTTTCG	CTGCAGAGTG	TAGATCCCAA	AAATTACCCA	AAGAAGAAGA
6228	TGGAAAAGCG	ATTTGTCTTC	AACAAGATAG	AAATCAATAA	CAAGCTGGAA	TTTGAGTCTG
6288	CCCAGTTCCC	CAACTGGTAC	ATCAGCACCT	CTCAAGCAGA	AAACATGCCC	GTCTTCCTGG
6348	GAGGGACCAA	AGGCGGCCAG	GATATAACTG	ACTTCACCAT	GCAATTTGTG	TCTTCCTAAA
6408	GAGAGCTGTA	CCCAGAGAGT	CCTGTGCTGA	ATGTGGACTC	AATCCCTAGG	GCTGGCAGAA
6468	AGGGAACAGA	AAGGTTTTTG	AGTACGGCTA	TAGCCTGGAC	TTTCCTGTTG	TCTACACCAA
6528	TGCCCCAAGT	CCTGCCTTAG	GGTAGTGCTA	AGAGGATCTC	CTGTCCATCA	GCCAGGACAG
6588	TCAGCTCTCT	CCTTTCAGGG	CCAATCCCCA	GCCCTTTTGT	TGAGCCAGGC	CTCTCTCACC
6648	TCTCCTACTC	ACTTAAAGCC	CGCCTGACAG	AAACCACGGC	CACATTTGGT	TCTAAGAAAC
6708	CCTCTGTCAT	TCGCTCCAC	ATTCTGATGA	GCAACCGCTT	CCCTATTTAT	TTATTTATTT
6768	GTTTGTTTGT	TTTGATTTCAT	TGGTCTAATT	TATTCAAAGG	GGGCAAGAAG	TAGCAGTGTC
6828	TGTAAAAGAG	CCTAGTTTTT	AATAGCTATG	GAATCAATTC	AATTTGGACT	GGTGTGCTCT
6888	CTTTAAATCA	AGTCCTTTAA	TTAAGACTGA	AAATATATAA	GCTCAGATTA	TTTAAATGGG
6948	AATATTTTATA	AATGAGCAAA	TATCATACTG	TTCAATGGTT	CTGAAATAAA	CTTCACTGAA
7008	GAAAAAATAA	AAAGGGTCTC	TCCTGATCAT	TGACTGTCTG	GATTGACACT	GACAGTAAGC
7068	AAACAGGCTG	TGAGAGTTCT	TGGGACTAAG	CCCACTCCTC	ATTGCTGAGT	GCTGCAAGTA
7128	CCTAGAAATA	TCCTTGGCCA	CCGAAGACTA	TCCTCCTCAC	CCATCCCCTT	TATTTCTGTTG
7188	TTCAACAGAA	GGATATTCAG	TGCACATCTG	GAACAGGATC	AGCTGAAGCA	CTGCAGGGAG
7248	TCAGGACTGG	TAGTAACAGC	TACCATGATT	TATCTATCAA	TGCACCAAAC	ATCTGTTGAG
7308	CAAGCGCTAT	GTAAGTAGGAG	CTGGGAGTAC	AGAGATGAGA	ACAGTCACAA	GTCCCTCCTC
7368	AGATAGGAGA	GGCAGCTAGT	TATAAGCAGA	ACAAGGTAAC	ATGACAAGTA	GAGTAAGATA

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7428 GAAGAACGAA GAGGAGTAGC CAGGAAGGAG GGAGGAGAAC GACATAAGAA TCAAGCCTAA
7488 AGGGATAAAC AGAAGATTTC CACACATGGG CTGGGCCAAT TGGGTGTCTGG TTACGCCTGT
7548 AATCCCAGCA CTTTGGGTGG CAGGGGCAGA AAGATCGCTT GAGCCCAGGA GTTCAAGACC
7608 AGCCTGGGCA ACATAGTGAG ACTCCCATCT CTACAAAAAA TAAATAAATA AATAAAACAA
7668 TCAGCCAGGC ATGCTGGCAT GCACCTGTAG TCCTAGCTAC TTGGGAAGCT GACACTGGAG
7728 GATTGCTTGA GCCCAGAAGT TCAAGACTGC AGTGAGCTTA TCCGTTGACC TGCAGGTCGA
7788 C

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Figure 3. DNA Sequence of the human IL-1RN gene. (GenBank Accession No. X64532)

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-5988 GTCGACCTGC AGGTCAACGG ATCTGAGAGG AGAGTAGCTT CTTGTAGATA ACAGTTGGAT
-5928 TATATACCAT GTCCTGATCC CCTTCATCAT CCAGGAGAGC AGAGGTGGTC ACCCTGATAG
-5868 CAGCAAGCCT GGGGGCTGCA GCTTGGTGGG TAGAGGTACT CAGGGGTACA GATGTCTCCA
-5808 AACCTGTCTT GCTGCCTTAG GGAGCTTCTA ATAAGTTGAT GGATTTGGTT AAAATTAAC
-5748 TGGCTACTTG GCAGGACTGG GTCAGTGAGG ACCAACAAAA AGAAGACATC AGATTATACC
-5688 CTGGGGGTTT GTATTCTTTG TGTTCCTTTC TCTTCTTTGT ACTAAAATAT TTACCCATGA
-5628 CTGGGAAAGA GCAACTGGAG TCTTTGTAGC ATTATCTTAG CAAAAATTTA CAAAGTTTGG
-5568 AAAACAATAT TGCCCATATT GTGTGGTGTG TCCTGTGACA CTCAGGATTC AAGTGTGGC
-5508 CGAAGCCACT AAATGTGAGA TGAAGCCATT ACAAGGCAGT GTGCACATCT GTCCACCCAA
-5448 GCTGGATGCC AACATTTTAC AAATAGTGCT TGCCTGACAC AAATGCAGT CCAGGAGGCC
-5388 CAAATGAAAA TGTTCGTACT GAAATTTGTT AAAGCTTCCC GACAAACTAG ATTTATCAGT
-5328 AAGGATTGTT TTCTGCAAGG GGGATGAAAC TTGTGGGGTG AGCCATTTGG GCTGAGGAGG
-5268 AGGGAGGTTG GAGCTGAGAA ATGTGGAGAC AATTTCCCTT TAGAAGGACT GAATCTCCCT
-5208 GCCTCTCTGG GGTGCGGCAG CCAGCAGGAT CCAATGGTGT ATATGTCTCC CCAGCTCCCC
-5148 ATTCAGTGAT ATCATGTCAG TAGCTTGAAA TTATCCGTGG TGGGAGTATT ATGTCATGGA
-5088 AATTGGCAAA TGGAAACTTT TATTGGAGAT TCAATTGTTA AACTTTTACC AGCACAACAC
-5028 TGCCCTGCCT TCAGAGTCAA TGACCCATC CAAGTTTAAT CCATCTGTCC ACTGTCTCCA
-4968 ACACGATCTT TATAAAACAC ACCTGACAAC ATTACCCTTT TATTCAGTTT TTTAAAAGAT
-4908 AAGTTTCCAG CTCATCGGGG TGGCTTTAAA GGCCATTTCT CCTCTGGACC TCACCCAAC
-4848 TTTCAAATCA CTTTTCCTAC CCCTACCTCT AAATGCTACT CAAACTCCAG CCATCCTGAA
-4788 TAATAAGACT TTTGAAAAGT AGATTATGGG CTGGGCACAG TGGCTCACAC CTGTAATCCC
-4728 AGCACTTTGG GAGGCCAAGA TGGGTGGATC ACCTGAGGTC GGGAGTTCGA GACCAGCCTG
-4668 ACTAACATAG TGAAACCCTG TCTCTACTAA AAATACAAAA TTAGTTGGGG GTGGTGGCAC
-4608 AAGCCTGTAA TCCCAGCTAC TCAGGAGGTT GAGGCAGGGG AATTGCTTGA ACCTGGGAGG
-4548 CGGAGGTTGC GGTGAGCCTA GATTGCTCCA CTGCACTCCA GCCTGGGCAA CAAGAGCGAA
-4488 ACTCCATCTC AAAAAAATAA ATAAATAAAT AAAGTAGATT ACATCAGATA CCTCTGGCCT
-4428 AGGTTGTTTA TGACCAACTC TCCTGCTGAG AATAACTAGA AAAGCTAGAC AAAACATATT
-4368 TCCAAAAGAT CTCTTTGGAG GCATCAGAGA ATGGCCAAGG CTGTAAGGAA CTGCCTGAGC
-4308 CCAGAGAGGT GGAGCCAGC ACTGGTGCCC TTTACTCCTG GGGACATGTG CTGGTTTCAA
-4248 AAACCTCAGC TGAGCTTTTG AGCATTCATG GAACTTGGTG GGGGAGATGA AATTGTACC
-4188 TTAAATCCTG CCTACAGGGA GGGTCCCTGA TAATCCCCAC CCAATTTGGA AATCTGGGTC
-4128 AGCCTTCACA GGTACTGAAG CCCTCCTCTG AATGATCTCA AGTCCTGCTA GGGTAGAGGT
-4068 TACCTGCTTT TGAAAGGCTC CTGGCCTACC TGTGCAGCAG GAGCAAAAGT GAACCATCTC
-4008 AGGGTACAGA TAACAATCAT CCAGAGCCTT GAATGACCTC TACTGTGCTT AATATATAGT
-3948 ATTCAGCAGT CAGTAAAAAG GATTTAGGCA CATGCAAGAT GACCTGTGTA TCAGGGAGAA
-3888 ATAGGCAATA AATTGAGATC CAGCAGGGAT TTGAATCATG GATTTGAATC AGGGGCAGCC
-3828 TTCGAAAGAA CTATGGAGAA TATACTCAGA TTTAAACAT AAGATTGGAA TTTTGGCAG
-3768 AGAACTAACA ACTGTACAAA AAAGGAACCA AATGGAAATC CTAGAAGTGA AAGATGCAAT
-3708 TAACCGATGT TGAGAAATAG CCAACATCTA TTGAACACTT CCCATGTGGA CAGCTGTGCT
-3648 AAACACTTTA CAGGCATCAA CATAAGATGT GTCCCCTTAC AGCAGTGCAG TGTCCCTCCT
-3588 AAGACATGGA CAGCCTGGTT TCCCTATCTC TCTGCTTCAT CAAAACCCCT TTACGTGGGG
-3528 CTTAGACACT CCTGTTGTCT CTAGTGTCTA GTAGCACAGG GCTCAGCACA TGGAAGCCAC
-3468 TAGATACAAT TTGATGACCA GGACCTCCGA TGAAAGCCAT GGGTGCTGAT TGGGAAGGCA
-3408 TTGTCTTTTA TGTGCTATGG TCTTAAAGCT TCATCCAGGA AGCAGAACTC GGGGGGTGCT
-3348 GAGGACCCAG AACCGAGAAT AAGATTAGTC AGAGATTTCC TGTGGGCAGA AATCATAAGG
-3288 ACGCCAACTG TTTGGGTGAG ATAAGACGAA ACCAAGAGTG GACTTGTGGC CAGAAGCGTG
-3228 AGGAAGAGGG AGAGAGCTTC CCTTGTCCCC TTTCTTCCTC TCCCTAAGCC ACAGTGATTG
-3168 ACAGCCCCCC CGCTTTGGAG TCAGAGCAGG CTTGAGACTG GACTGGGAAA GGAGGGTGGG
-3108 TCAGGATACA GAGCAGGAAG GCTGGGAGTG CAGGGCAGGA GCAAGGGGCT GGGGCATTCA
-3048 TTGTGCCTGA TCTCTCCAC TTTACCTGGG GTAAAGAAGC ATATGCAAAA GCCACGGTGT

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-2988	GAGTATTTCC	CAAGTGCCAG	GGTCAGGGCA	TGATTTCATCA	CGTGCAGCAT	TTCATTCAAT
-2928	CCTTATAGTA	ACCGATGATG	TGGCTTCTAT	TATTAGCTCT	ATCAGATAAT	GAAACTGAGA
-2868	CCAAGACAGG	CTCTGCACAT	TGTGTGGGGT	AATGACACAG	GGGGATTTCAG	ACCTAGACTC
-2808	CATAACTCCT	GCCCCAGGGA	CCACCCCCAC	CCTCACCTTG	TGCATGTCTGA	CAAAGGACAG
-2748	ACTGGGCCAC	TTCTCAGGAC	ACAGCGGGGA	AATGACACAG	AGCAGGGAGG	TTCCAGGAGC
-2688	CCCGAGCGTC	TTTTCTCCAG	GAGAATACTC	TCTGAATTCA	GACTGGGGTC	AGAGAAACAT
-2628	TTACCCAGGA	GCCGCAGTGT	GGGTGGGGCT	TTTTACTTGA	AACGCTGTCT	GAAGGCAGTG
-2568	GCAGGATGAA	CTCTCCACCC	TACCTTGGCA	AGCCACTTCT	CTTCTGCAAT	CTGTAAGGAC
-2508	ATTGTTGAGA	GAATTATGGT	CTTCCAATTC	CGGAGGGTTG	AAGAAAGACA	AATAGGAGAG
-2448	AACCTATCAT	AGTCAGGTGC	TAGCTGCCTT	CTCTTTTCAGA	GAGTGTGAGA	ATAAAGTGAT
-2388	ACACTTGATT	ATTAGCAAAT	ACTTTGGAAA	TTTTAAACGC	TAATATTCAA	CACACTCTGG
-2328	AAGAGGCAAA	TAAGTAGACA	GGTTCATATA	CATCATCTCC	TTCAGCTAGT	CCTCACAAAA
-2268	ACAAACAAAT	GAATAAACAA	AATTCTTCTT	TGGCCCTCAT	AGGAAGACAC	TGTTTCTTGA
-2208	ACGTGTTTCA	AAAAGGATGG	GTGACTCACT	CAAGGTCACA	CTGTTTATGA	GGACAGTACA
-2148	GGAATACAGA	CATGCCATTT	TGCCTGAAAA	AATCCATCAC	CCAGGGAGGT	GACACAATTT
-2088	TGCAGAAATG	TTCTATTTCC	TCTGAAGGAT	ACATTCTTTA	AACCTTTGGG	AAATTCATTC
-2028	ATAGTCTTCC	TCCTTTGAAG	GATTACTCTC	TGGACACAAA	GTGTTTGATT	CTGATTTGTT
-1968	GGTTGGAAGA	TGTGTTGGTT	GAGAGAAAGA	TTCTGATTTG	TTGGTTGAAA	ATAGACTCAT
-1908	CAAGATCAAC	TGCTGTAGTA	GTAATATTTT	TGACATTTTG	TCTGTATTCC	TGTGCTGCCC
-1848	TCACAAGCTG	CATCACCTTG	AGTGAGTCAT	TCATACTTTT	TTGTTTGTTT	TTGTTTGGGA
-1788	GATGGAGTCT	TACTCTGTTG	CCTAGGCTGG	AGTGCGGTGG	CGTGATCTTG	GCTCACTGCG
-1728	ACCTCCATCT	CCTGGGTTCA	AGTGATCCTC	CTGCCTCAGC	CTCCCGAGTA	GCTGGGATTA
-1668	CAGGCACATG	CCACCATCCC	TGCTAATTTT	TGCATTTTCA	GTAGAGACGG	AGTTTCACCA
-1608	TGTTGGTCAG	GTTGGTCTTG	AACTCCTGAC	CTCAGGTGAT	CCGCCCCACCT	CAGCCTCCCC
-1548	AAGTGCTGGG	ATTACAGGTG	TGAGCCACCG	TGCCCAGCCC	AGCCATCATT	TTTGAAACAC
-1488	GTTTGAGAAA	TAGTGTCTTC	CTTTGAGGGC	CAAGGAGACA	TTTTTTTTTG	TTATTTGTTT
-1428	GTTTTTGTGA	GGACTAGCTG	AAGGGGGTGA	TGTATATTAA	CCTGCCTACT	TATTTGCCTC
-1368	TTCCCAGAGT	GTGATGAATA	TTAGGGTTTA	AAGTTTCTGA	AGCATTGTGT	AATAAAGCCC
-1308	GGGGCTGGAG	GTCAGAAGAC	CTGGATTTCT	CTGCATACTT	TTGCCATCAG	CAAGCTGTGT
-1248	GACCTGGGAC	AGATCCCTTT	TTTGTCTAAA	TCTTTCTGAG	TCTTCTTGAA	AACAATGCCA
-1188	GGTTGGGACA	GGATGATTGC	CAAGCTCCCG	TCCAGCTCTA	AAACACTGCA	ACGTATGCTT
-1128	CTGCACCAGC	ACTGTCCATC	CTGTAGATCA	TGCAGAAATT	CTCTTCAACT	TTTTCTTACC
-1068	CATAAAATAG	GAGCATGCTT	ACCTTTTCTC	TAATGTTCCA	GGCCCCGGGT	CTAGATATTG
-1008	TAAGTAAGGA	AGTTAATGTG	TATCAGAGCC	CATTATGGGC	CAGAAGTTCT	CCTCTTCCCT
-948	CCTACACCTG	CTTCCCTCCCT	CCCTCCCTCC	CTCTTTCCCT	TCCTTCCCTC	CATCCATTTG
-888	TGAAGAAGAC	ATGATCACCC	TCATTCTGAG	AGTGAAGAGA	CAGAGGCTCA	ACTAATGAAA
-828	TGATTTGTTC	AAGGTCACAC	GGGTGGCACA	AGGCAAGTGG	CAGAGGTTGA	ATTTAGACCC
-768	ATTCTGTGCC	AAATGCTGAG	TTTATGTCAT	CGTCCCGAGA	CCATAACTTT	AAAGATGTAA
-708	GATAGTGGGA	AAAGAGTTGA	TTTCAAAGCA	CCTCTCAGAA	GGACTCACTT	TACATCAGGG
-648	GTCAGCAGAC	TCAGGCCAAA	TCCGGTCCAT	TCCCCGCTTT	TGCAAAGAAA	GTTGTAGTGG
-588	AACACAGCTA	GGCTTATTGA	TTTATGGATT	GCCAACGTCC	TTTTGTGAAA	CAGACAGCTG
-528	AGCTGAGTAA	TCGTGGCGCA	CAAAACCTAA	AATATTTACT	ATCTCGTCCT	TTACAGAATG
-468	TTTGCCAATC	TATGGTCCGG	AGTCCAAGGC	TGTCCATTTT	TCAAAGAACA	CAAAGTGACA
-408	TGAGACTGTC	CCATGTGCAG	GGAGCCCTAT	CATTTTATTA	TGAAAAAACG	GCCTTTCTGC
-348	TCAAATCTGT	TTTTTAAAAA	GTCAACAAAC	AGACTCTGGG	TACCTGTCAG	GAACAGTAGG
-288	GAGTTTGGTT	TCCATTGTGC	TCTTCTTCCC	AGGAACTCAA	TGAAGGGGAA	ATAGAAATCT
-228	TAATTTTGGG	GAAATTGCAC	AGGGGAAAAA	GGGGAGGGAA	TCAGTTACAA	CACTCCATTG
-168	CGACACTTAG	TGGGGTTGAA	AGTGACAACA	GCAAGGGTTT	CTCTTTTTTG	AAATGCGAGG
-108	AGGGTATTTT	CGCTTCTCGC	AGTGAGGCAG	GCTGGCAGAC	GCCTAGCTTG	GGTGAGTGAC
-48	TATTTCTTTA	TAAACCACAA	CTCTGGGCCC	GCAATGGCAG	TCCACTGCTT	GCTGCAGTCA
13	CAGAATGGAA	ATCTGCAGAG	GCCTCCGCAG	TCACCTAATC	ACTCTCCTCC	TCTTCTCTGT
73	CCATTCAGAG	ACGATCTGCC	GACCCTCTGG	GAGAAAATCC	AGCAAGATGC	AAGCCTTCAG
133	GTAAGGCTAC	CCCAAGGAGG	AGAAGGTGAG	GGTGGATCAG	CTGGAGACTG	GAAACATATC

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193	ACAGCTGCCA	GGGCTGCCAG	GCCAGAGGGC	CTGAGAACTG	GGTTTGGGCT	GGAGAGGATG
253	TCCATTATTC	AAGAAAGAGG	CTGTTACATG	CATGGGCTTC	AGGACTTGTTG	TTTCAAAATA
313	TCCCAGATGT	GGATAGTGCG	ACCGGAGGGC	TGTCTTACTT	TCCCAGAGAC	TCAGGAACCC
373	AGTGAGTAAT	AGATGCATGC	CAAGGAGTGG	GACTGCGATT	CAGGCCTAGT	TGAATGTGCT
433	GACAGAGAAG	CAGAGAGGGG	CACCAGGGGC	ACAGCCCGAA	GGCCAGACT	GATATGGGCA
493	AGGCCTGTCT	GTGCTGACAT	GTCGGAGGGT	CCCCTCTCC	AGGGACCTTG	GTTTCCCCGT
553	CTGTGACATC	TGTGACATGA	GAGTCACGAT	AACTCCTTGT	GTGCCTTACA	GGGTGTTGT
613	GAAAATTAAA	TGCACAGATA	ATAGCGTAAC	AGTATTCCGT	GCATTGTAAA	GAGCCTGAAA
673	ACCATTATGA	TTTGAAAATG	GAATCGGCTT	TGTGAGACCA	TCACTATTGT	AAAGATGTGA
733	TGCTGATAGA	AATGACAGGA	CTGCTTGTGC	ATGCCCTCTG	CAGTGTGACA	TTCCAGCAGT
793	GAAATCATGT	TGGGGTGACT	TCTCCCCCAC	TCTGACCTTT	ATGTTTGTCT	GGGCCGAGGC
853	TGCAAGTCGG	GCTCTGTGGG	TGTATGAGTG	ACAAGTCTCT	CCCTTCCAGA	TATGGGGACT
913	GTCTGCTTCC	CTAGGTTGCC	TCTCCCTGCT	CTGATCAGCT	AGAAGCTCCA	GGAGATCCTC
973	CTGGAGGCCC	CAGCAGGTGA	TGTTTATCCC	TCCAGACTGA	GGCTAAATCT	AGAACTAGG
1033	ATAATCACAA	ACAGGCCAAT	GCTGCCATAT	GCAAAGCACT	TTGGTTTGCC	TGGCCACCCC
1093	TCGTCGAGCA	TGTGGGCTCT	TCAGAGCACC	TGATGAGGTG	GGTACAGTTA	GCCACACTTC
1153	ACAGGTGAAG	AGGTGAGGCA	CAGGTCCCAG	GTCAGGCTGG	CCGGAGCTCT	GTTTATTACG
1213	TCTCACAGCT	TTGAGTCCTG	CTCTCAACCA	GAGAGGCCCT	TTACCAAGAA	GAAAGGATTG
1273	GGACCCAGAA	TCAGGTCACT	GGCTGAGGTA	GAGAGGAAGC	CGGGTTGTTT	CCAAGGGTAG
1333	CTGCTCCTGC	AGGACTCTGA	GCAGGTCACC	AGCTAATGGA	GGAAAGGCTC	TAGGGAAAGA
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1993	ATCTGAGGAA	CAACCAACTA	GTTGCTGGAT	ACTTGCAAGG	ACCAAATGTC	AATTTAGAAG
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2233	TGAAGAGGGT	GTGGAGAGGT	AGAGTCTAGG	TCAGAGGTCA	GTGCCTATAG	GCAAGTGGTC
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2413	TCCACCATGT	ATAAGGTTGA	GCTATGTCTC	TTATTCCCTG	ACACCATACT	CAGCCATATC
2473	TGGTCCACAC	ATTAACAGCT	GGATGACCTT	GAAGAAGCTT	CACCCACTCT	GTTCCCTCAG
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2593	CCTTCCAGGA	TGTTTTCACT	CCCCTGTTTG	TTGTTGTAGG	ATGGTATTAC	CTCCACCTTC
2653	CCACCTTCCC	TATGCCCTGG	TTCTGTCTCC	TGTGCCTCGC	TCTGAAAGTG	GATGAGACCT
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2773	TTTGTTGCTA	CATGAGAGCA	TGGAGGCCTC	TTAGGGAGAG	AGGAGGTTCA	GAGACTCCTA
2833	GGCTCCTGGT	GGAGCCCCAC	TCATGGCCTT	GTTTATTTTC	CCTGCCCTTC	AGCAACACTC
2893	CTATTGACCT	GGAGCACAGG	TATCCTGGGG	AAAGTGAGGG	AAATATGGAC	ATCACATGGA
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3013	TGAGGGAAAT	ATGGACATCA	CATGGAACAA	CATCCAGGAG	ACTCAGGCCT	CTAGGAGTAA
3073	CTGGGTAGTG	TGCATCCTGG	GGAAAGTGAG	GGAAATATGG	ACATCACATG	GAACAACATC
3133	CAGGAGACTC	AGGCCTCTAG	GAGTAACTGG	GTAAGTGCA	TCCTGGGGAA	AGTGAGGGAA
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3253	TGTGCTTGGT	TTAATCTTCT	ATTTACCTGC	AGACCAGGAA	GATGAGACCT	CTCTGCCCTT
3313	CTGACCTCGG	GATTTTAGTT	TTGTGGGGAC	CAGGGGAGAT	AGAAAAATAC	CCGGGGTCTC

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3373	TTCATTATTG	CTGCTTCCTC	TTCTATTAAC	CTGACCCTCC	CCTCTGTTCT	TCCCCAGAAA
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4213	TGTCTCAGGG	GCTTGCTGGA	TGCAACCTTA	ACCTCAATGT	GAGTGGCCAT	ACTGTGGCAC
4273	TGTCCCATCC	CTCACCAGGG	ACACTGTTCT	GGAGGGTGAC	TGCCTGTTCT	GTGAGGAGTG
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4693	GTGTGGTGGT	GCATGCCTGT	AATCCCAGCT	ACTCAGGAGG	CTGAGGCAGG	AGAATCGCTT
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5353	GGACCAGCCA	TTGAGGGGTG	GACCCTCAGA	AGGCCTCACA	ACAACCTGGT	CACAGGACTC
5413	TGCCTCCTCT	TCAACTGACC	AGCCTCCATG	ATGCCTCCAG	AATGGTCTTT	CTAATGTGTG
5473	AATCAGAGCA	CAGCAGCCCC	TGCACAAAGC	CCTTCCATGT	CGCCTCTGCA	TTCAGGATCA
5533	AACCCCGACC	ACCTGCCCAA	CCTGCTCTCC	TCTTGCCACT	GCCTCTTCCT	CCCTCATTTCC
5593	ACCTTCCCAT	GCCCTGGATC	CATCAGGCCA	CTTGATGACC	CCCAACCAAG	TGGCTCCAC
5653	ACCCTGTTTT	ACAAAAAGA	AAAGACCAGT	CCATGAGGGA	GGTTTTTAAG	GGTTTGTGGA
5713	AAATGAAAAT	TAGGATTTC	TGATTTTTTT	TTTTTCAGTCC	CCGTGAAGGA	GAGCCCTTCA
5773	TTTGAGGATT	ATGTTCTTTC	GGGGAGAGGC	TGAGGACTTA	AAATATTCCT	GCATTTGTGA
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5893	CAACTTGTA	AAATTAAG	TTATGGTACT	ATGTTAGCCC	CATAATTTTT	TTTTTCCTTT
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6073	TCAGTCCCA	AGGCTCTGAG	CAAATGTGGC	TCCTGGGGGT	TCTTTCTTCC	TCTGCTGAAG
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6193	GCTGTGCCTC	TGCCTGTCTC	CCCACGAGC	TGGGAGCTCT	GCAGAGCAGG	AAACATGACT
6253	CGTATATGTC	TCAGGTCCCT	GCACGGCCAA	GACACTAGCC	TCGCTCTTGG	CAGGTACTCA
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6373	TTTTACAATA	AAATCTTGAA	AATGCCTATA	TTGTTGACTA	TGTCCTTGGC	CTTGACAGGC
6433	TTTGGGTATA	GAGTGCTGAG	GAAACTGAAA	GACCAATGTG	TYTTYCTTAC	CCCAGAGGCT
6493	GGCGCCTGGC	CTCTTCTCTG	AGAGTTCTTT	TCTTCCTTCA	GCCTCACTCT	CCCTGGATAA

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6553 CATGAGAGCA AATCTCTCTG CGGGG

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(21) International Application Number: PCT/US98/23721 (22) International Filing Date: 9 November 1998 (09.11.98) (30) Priority Data: 9723553.5 7 November 1997 (07.11.97) GB 09/005,923 12 January 1998 (12.01.98) US (71) Applicant (for all designated States except US): MEDICAL SCIENCE SYSTEMS, INC. [US/US]; 3567 Shaw Avenue, Cincinnati, OH 45208 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DUFF, Gordon, W. [GB/GB]; 18 Ashgate Road, Sheffield, South Yorkshire S10 3B2 (GB). GIOVINE, Marco [GB/GB]; 18 Ashgate Road, Sheffield, South Yorkshire S10 3B2 (GB). BARNES, Peter, J. [GB/GB]; Imperial College School of Medicine at The National Heart & Lung Institute, Dept. of Thoracic Medicine, Dovehouse Street, London SW3 6LY (GB). LIM, Simon [GB/GB]; Imperial College School of Medicine at The National Heart & Lung Institute, Dept. of Thoracic Medicine, Dovehouse Street, London SW3 6LY (GB). (74) Agents: ARNOLD, Beth, E. et al.; Foley, Hoag & Eliot, LLP, One Post Office Square, Boston, MA 02109 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 16 September 1999 (16.09.99)	

(54) Title: DIAGNOSTICS AND THERAPEUTICS FOR CHRONIC OBSTRUCTIVE AIRWAY DISEASE

(57) Abstract

Methods and kits for detecting polymorphism that are predictive of a subject's susceptibility to developing a chronic obstructive airway disease as well as the relative severity of the disease are described.

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INTERNATIONAL SEARCH REPORT

Int .tional Application No

PCT/US 98/23721

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 97 06180 A (MEDICAL SCIENCE SYSTEMS INC ;KORNMAN KENNETH S (US); DUFF GORDON W) 20 February 1997 (1997-02-20) claims 1-8	1-15
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

26 July 1999

Date of mailing of the international search report

02/08/1999

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Osborne, H

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International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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